Synthesis and Biological Evaluation of a Furanosteroid Library of PI3-kinase Inhibitors and Studies Toward the Total Synthesis of 9-Normethylpleurotin

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Synthesis and Biological Evaluation of a Furanosteroid Library of PI3-kinase Inhibitors and Studies Toward the Total Synthesis of 9-Normethylpleurotin

Julia Vargas, M.S.

University of Pittsburgh, 2009

A library of furanosteroids was synthesized by oxidation of a catechol and a 4-hydroxycoumarin with potassium ferricyanide. Further diversification of these substrates was achieved through various acetalization reactions. The resultant compounds were then evaluated as potential inhibitors against PI3-kinase using a competitive ELISA assay. As an extension to this initial library, a subset of cromolyn derivatives were synthesized and subsequent biological evaluation of these compounds is underway. Secondly, studies have been ongoing to achieve the total synthesis of pleurotin featuring an *in situ* hydrozirconation-transmetallation-aldehyde addition process followed by an Ireland-Claisen rearrangement and finally an intramolecular Diels-Alder cyclization. Previous difficulty with the installation of the C_8-C_9-C_{21} side-chain and the configuration at the C_{10} center led us to pursue the 9-normethylpleurotin analog. In our efforts to address this stereochemistry issue difficulties arose in scaling up the initial route to our key starting aldehyde for the hydrozirconation-transmetallation-aldehyde addition. Therefore an alternative route was developed utilizing a benzyne-furan [4 + 2]-cycloaddition.

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AIBN	Azobisisobutyronitrile
DIPEA	Diisopropylethylamine
DLP	Lauroyl peroxide
DMAD	Dimethylacetylene dicarboxylate
DMAP	4-Dimethylamino pyridine
DMF	N',N'-Dimethylformamide
DMP	Dess-Martin periodinane
HMBC	Heteronuclear multiple bond correlation
HMQC	Heteronuclear multiple quantum coherence
KOH	Potassium hydroxide
m-CPBA	*meta*-Chloroperoxybenzoic acid
MOMCl	Methyl chloromethylether
NaH	Sodium hydride
PI3K	Phosphatidylinositol-3 kinase
PIDA	Phenyliodonium diacetate
PIFA	Phenyliodoium *bis*(trifluoroacetate)
Py	Pyridine
SIBX	Stabilized 2-iodoxybenzoic acid

TBAI	Tetrabutylammonium iodide
THF	Tetrahydrofuran
Trx	Thioredoxin
TrxR	Thioredoxin reductase

1.0 SYNTHESIS AND BIOLOGICAL EVALUATION OF FURANOSTEROID LIBRARY AS PI3-KINASE INHIBITORS

1.1 INTRODUCTION

Phosphatidylinositol 3-kinases (PI3Ks) are members of a widely expressed enzyme family that catalyzes phosphorylation at the 3-position of the inositol ring in phosphoinositides **(Figure 1)**.[1] The PI3K enzyme is found in cellular complexes containing ligand activated growth factor receptor and oncogene protein tyrosine kinases.[2] The PI3Ks are involved in the regulation of diverse cellular processes that are essential for cell growth and differentiation, including cell proliferation, cell survival, cytoskeletal organization, vesicle trafficking, glucose transport, and platelet function.[3] It has been shown that PI3K activity is elevated in response to platelet-derived growth factor (PDFG), insulin, insulin-like growth factor 1 (IGF-1), colony stimulating growth factor 1 (CSF-1), nerve growth factor (NGF), hepatocyte growth factor (HGF), stem cell growth factor, and epidermal growth factor (EGF).[2,4-6] The diverse range of PI3K functional effects are attributed to its activation by numerous receptors and the existence of multiple effector proteins that can interact with phosphatidylinositol (PtdIns) lipid products by different structural motifs.[6]

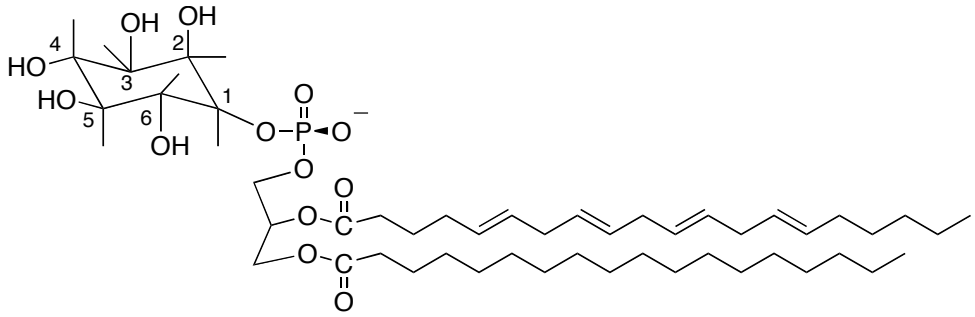


Figure 1. Structure of phosphatidylinositol (PtdIns)

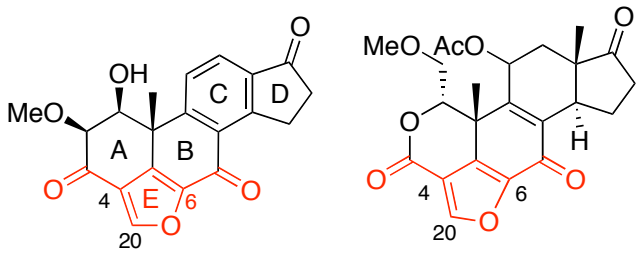
Table 1. PI3K Family Members

Class	Catalytic Subunit	Adaptor/Binding Partner	Distribution
IA	P110α	p85α, p50α, p55α	Broad
	P110β	p85β	Broad
	P110δ	p55γ	Leukocytes
IB	P110γ	p101	Leukocytes
II	PI3K-C2	Clathrin	Broad
III	PtdIns 3-Kinase	p150	Broad

The PI3Ks are divided into three classes based on structural homology and substrate specificity **(Table 1)**.[4,6] The most widely studied Class I enzymes are comprised of heterodimers and divided into two subclasses. Class Ia includes: three catalytic isoforms (p110α, p110β, p110δ) and five regulatory/adaptor isoforms (p85α, p85β and p55γ encoded by specific genes and p55a and p50a that are produced by alternate splicing of p85α).[6-9] Class Ib enzymes are comprised of a p110γ catalytic domain and a p101 adapter subunit and are expressed mainly in leukocytes.[6,7] Four different lipid products are generated from Class I PI3Ks: the singly phosphorylated form PtdIns-3-P, the doubly phosphorylated forms PtdIns-3,4-P_2 and PtdIns-3,5-P_2, and lastly, the triply phosphorylated form PtdIns-3,4,5-P_3.[10] The major products found within cells are PtdIns-3,4-P_2 and PtdIns-3,4,5-P_3 as they are transiently induced upon cell stimulation.[6] Both PtdIns-3,4-P_2 and PtdIns-3,4,5-P_3 selectively bind certain pleckstrin homology (PH)

domains, modular segments of 100 amino acids found in many signaling proteins.[6] It has been suggested that the specificity of PI3K signaling is due to the ability of PH domains to differentiate between the various PtdIns lipid products, as they are able to trigger and propagate downstream signaling events.[6] Class II PI3Ks are monomeric enzymes and are characterized by the presence of a C2 domain at the carboxyl-terminus.[6,9] They consist of broadly expressed PI3K-C2α and PI3K-C2β isoforms as well as the liver specific PI3K-C2γ isoform.[9] Class III PI3Ks are heterodimeric enzymes that consist of a p150 adaptor subunit and a PI3-Kinase producing catalytic subunit.[9]

Activation of the PI3K pathway is a feature common to a variety of human cancers. Both PI3K gene amplification and protein overexpression have been found in lung, breast, and ovarian cancer cells.[11,12] Activating mutations in the catalytic subunit of PI3K (p110α) have been found in breast, colorectal, and brain tumors.[12-16] The PI3K pathway is downregulated by the tumor suppressor protein phosphatase and tensin homoglogue (PTEN). Consequently, if a mutation or a deletion to PTEN occurs it leads to increased tumor growth, which has been seen in a striking number of human tumors.[17] The elucidation of downstream signaling events was largely achieved through the use of small molecule inhibitors such as wortmannin **(Figure 2).**[18] Studies have shown that wortmannin competes with ATP for binding to the PI3K catalytic domain irreversibly via a covalent interaction of a critical lysine residue.[18-20]



1
Viridin

2
Wortmannin

Figure 2. General scaffold for viridin class of natural products

Wortmannin **(2)** is a member of the viridin family of natural products that is comprised of several pentacyclic furanosteroids isolated as fungal metabolites from species such as *Gliocladium virens, Gliocladium deliquescen,* and *Penicillium wortmanni* **(Figure 2)**.[21,22] These furanosteroids not only possess antibiotic and antifungal properties, but they also inhibit various stages of cell signaling processes.[23] Members of the viridin class, such as viridin **(1)** and wortmannin **(2)** are characterized by their unusual steroid structure possessing a furan fused between the A and B rings, as well as an aromatic C-ring.[21] A key feature of this unique pentacyclic scaffold is the presence of two carbonyl groups flanking the furan moiety, which have been suggested to enhance the electrophilic nature of the ring system, contributing to its reactivity in biological systems.[22]

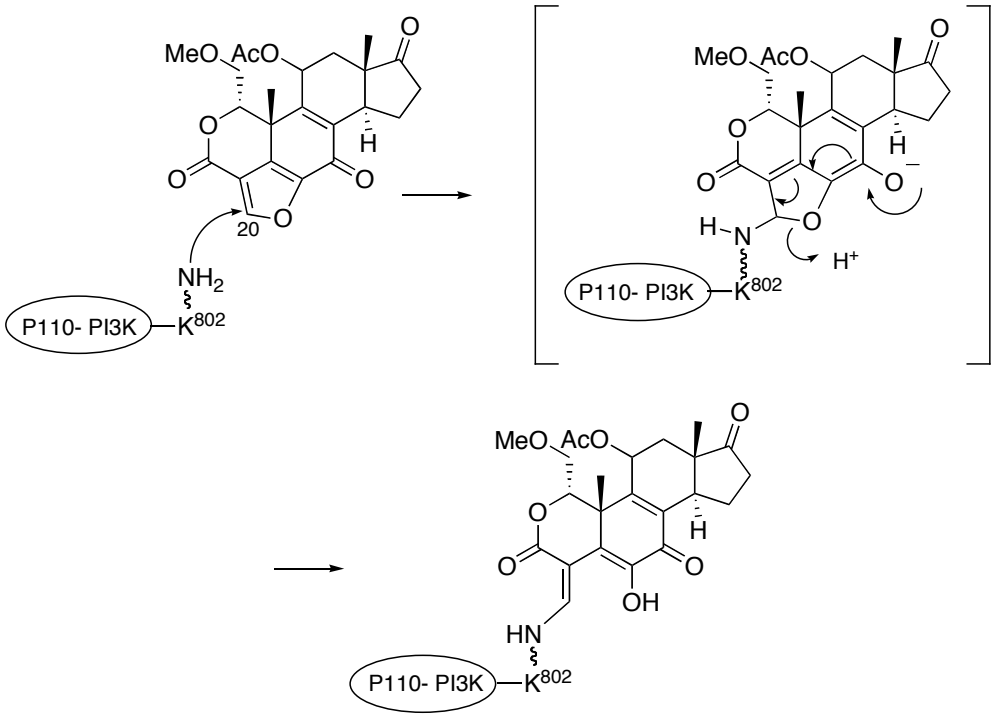


Figure 3. Proposed mechanism of action of PI3K inhibition by wortmannin

Wortmannin was first reported to be a potent anti-inflammatory agent, however later it was discovered to be a potent irreversible and selective inhibitor of PI3-kinase (IC_{50}= 4.2 nM).[19,20,22] The mechanism in which PI3K is suggested to interact with wortmannin involves attack of Lys^{802} of the catalytic site of p110α[18] and Lys^{883} of p110δ on the electrophilic C_{20} carbon **(Figure 3)**.[18,24] The Lys^{802} residue is found in the ATP-binding site of the p110 catalytic domain and therefore plays a critical role in the phosphotransfer reaction. Various structure activity relationship studies by Norman and co-workers support the susceptibility of nucleophilic attack at this C-20 position of wortmannin by both primary and secondary amines.[19,25,26]

In 2004, Wipf and co-workers synthesized a library of 94 synthetic viridins and a series of 5 C-20 thioether derivatives through the nucleophilic ring opening of Wortmannin at the C-20 position.[2] Each sample was screened for its ability to inhibit PI3-kinase and mTOR in a variety

of tumor cell lines by the Powis group and the National Cancer Institute. Among these initial compounds, ten of the most potent candidates were selected for further investigation. Within the subset of ten, the bis-allyl derivative PX-866 produced the most promising biological results as a potent, specific, and irreversible inhibitor of PI3-kinase, demonstrating a lower liver toxicity and greater promise for inhibition of cell growth over the lead structure wortmannin **(Figure 4)**.[2]

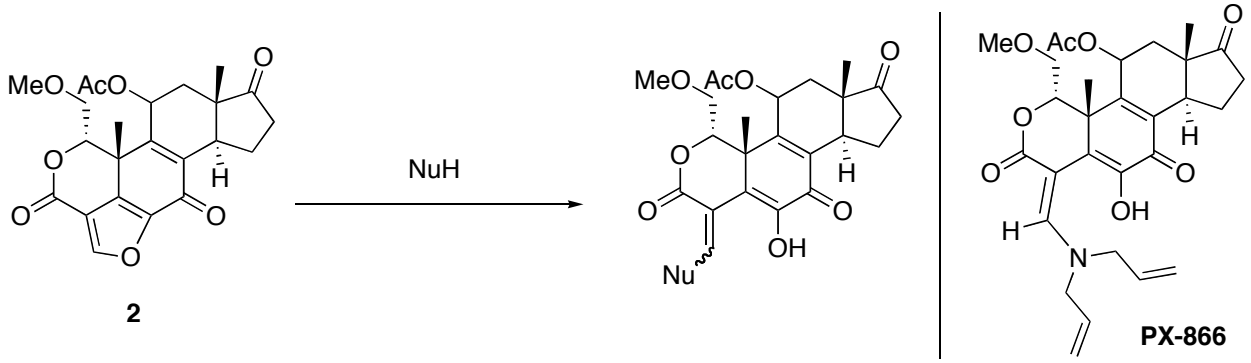


Figure 4. Synthetic viridins obtained via nucleophilic ring opening of wortmannin and the structure of PX-866

Since this discovery, PX-866 has been shown to be a biologically stable inhibitor of PI3-kinase *in vitro* and *in vivo*.[7,12,27] PX-866 has demonstrated oral efficacy and PI3K inhibition in numerous human xenografts models in mice.[7,12,27] It has also been shown that PX-866 enhances the antitumor activity of other chemotherapeutic drugs and radiation.[7,12] Most recently, in 2008, PX-866 entered phase I clinical trials and is being developed clinically as an oral formulation for patients with advanced solid metastatic tumors.

1.2 LIBRARY SYNTHESIS AND SCAFFOLD DIVERSIFICATION

Our interdisciplinary drug discovery program utilizes novel natural product scaffolds as the foundation of diversity oriented library synthesis.[2,28,29] The viridin class of compounds has been used as a benchmark for the development of selective kinase inhibitors. Our specific objectives for this library synthesis were to develop synthetic analogs containing the fused electrophilic benzofuran core similar to that found in wortmannin.

Recently, syntheses of related furanosteroids, the coumestans, have been reported using a variety of methods such as electrochemical oxidations,[30-32] Pd and Ag mediated cyclizations,[33-36] photochemical processes,[37] as well as enzymatic methods with tyrosinase[38] and laccase, a multicopper oxidase that are capable of oxidizing a variety of substrates while concomitantly reducing O_2.[39]

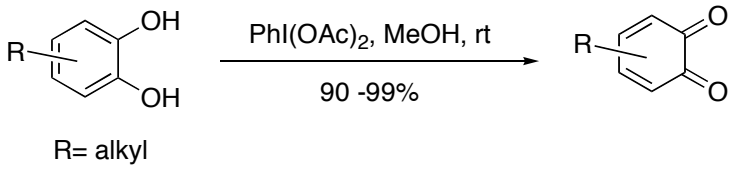
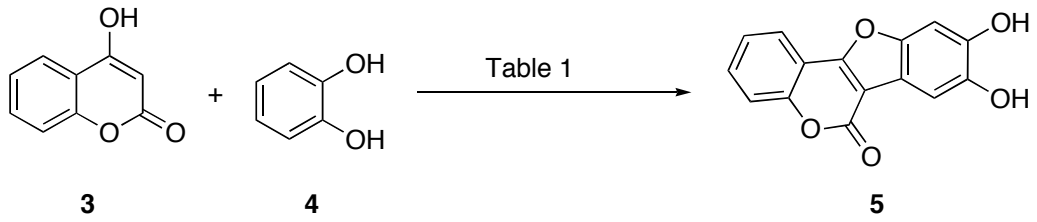


Figure 5. Oxidation of 1,2-dihydroxybenzenes with hypervalent iodine

Recent interest in the use of hypervalent iodine reagents for the oxidation of quinols to quinones **(Figure 5)**[40,41] led us to investigate their utility as reagents in our furanosteroid synthesis. We first screened a variety of hypervalent iodine reagents as oxidants in the intermolecular coupling of a 4-hydroxycoumarin and a catechol **(Scheme 1)**.



3 **4** **5**

Scheme 1. Reaction scheme for furanosteroid library synthesis

Table 2. Oxidation conditions screened for intermolecular condensation reaction

Entry	Oxidant (equiv)	Solvent	Conc. (M)	Time (h)	Comment
1	PIDA (2.0)	MeOH	0.5	24	messy rxn mixture
2	PIDA (1.0)	CH_3NO_2	0.25	24	messy rxn mixture
3	PIDA (1.0)	CH_3NO_2	0.5	5[b]	messy rxn mixture
4	PIDA (1.0)	CH_3CN	0.5	3	messy rxn mixture
5	PIDA (2.0)	CH_3CN	0.5	3	messy rxn mixture
6	PIDA (2.0)	CF_3CH_2OH	0.25	3	messy rxn mixture
7	PIDA (2.0)	CF_3CH_2OH	0.50	3	messy rxn mixture
8	PIFA (1.2)	CH_3CN	0.50	3[c]	no product observed
9	PIFA (1.2)	CF_3CH_2OH	0.10	3[c]	no product observed
10	PIFA (1.2)	CF_3CH_2OH	0.10	24	no product observed
11	PIFA (2.0)	CF_3CH_2OH	0.10	3[c]	no product observed
12	$NaIO_3$, py	EtOH/H_2O (9:1)	0.10	24	decomposition
13	SIBX	THF	0.05	24	decomposition
14	DMP	CH_2Cl_2	0.10	24	decomposition

[a]all reactions were run at rt unless otherwise noted; [b]reaction mixture was heated to 55 ^oC; [c]reaction mixture was cooled to 0 ^oC.

Utilizing phenyliodonium diacetate (PIDA) in a variety of solvents and concentrations all led to messy reaction mixtures and no product formation was observed by ^{1}H NMR analysis **(Table 2, Entries 1-7)**. Testing the more electron rich phenyliodoium *bis*(trifluoroacetate) (PIFA) under a range of conditions also gave messy reaction mixtures and no product was observed by ^{1}H NMR analysis **(Table 2, Entries 8-11)**. Attempts to oxidize with sodium iodate and pyridine,[42] stabilized 2-iodoxybenzoic acid (SIBX),[43-45] or Dess Martin Periodinane (DMP) all resulted in decomposition with trace starting material observed by ^{1}H NMR **(Table 2, Entries 12-15)**.

Due to the lack of success with the hypervalent iodine reagents, we used a procedure developed by Wanzlick et al. using $K_3Fe(CN)_6$ as the oxidant for the intermolecular condensation of catechol with 4-hydroxycoumarin.[46,47] In the 1960's, Wanzlick reported the use of both $K_3Fe(CN)_6$ and $NaIO_3$ reagents for the *in situ* generation of a quinone which then undergoes Michael addition of the present nucleophile to afford the respective coumarone products **(Figure 6)**.

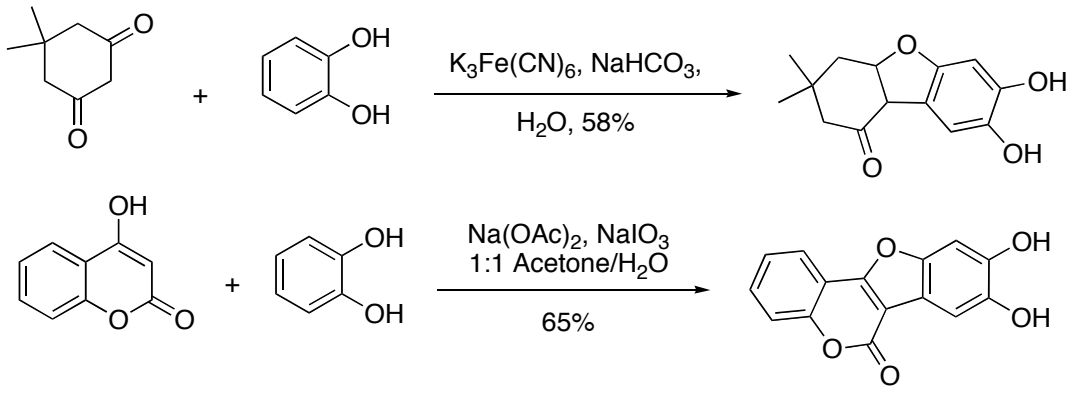
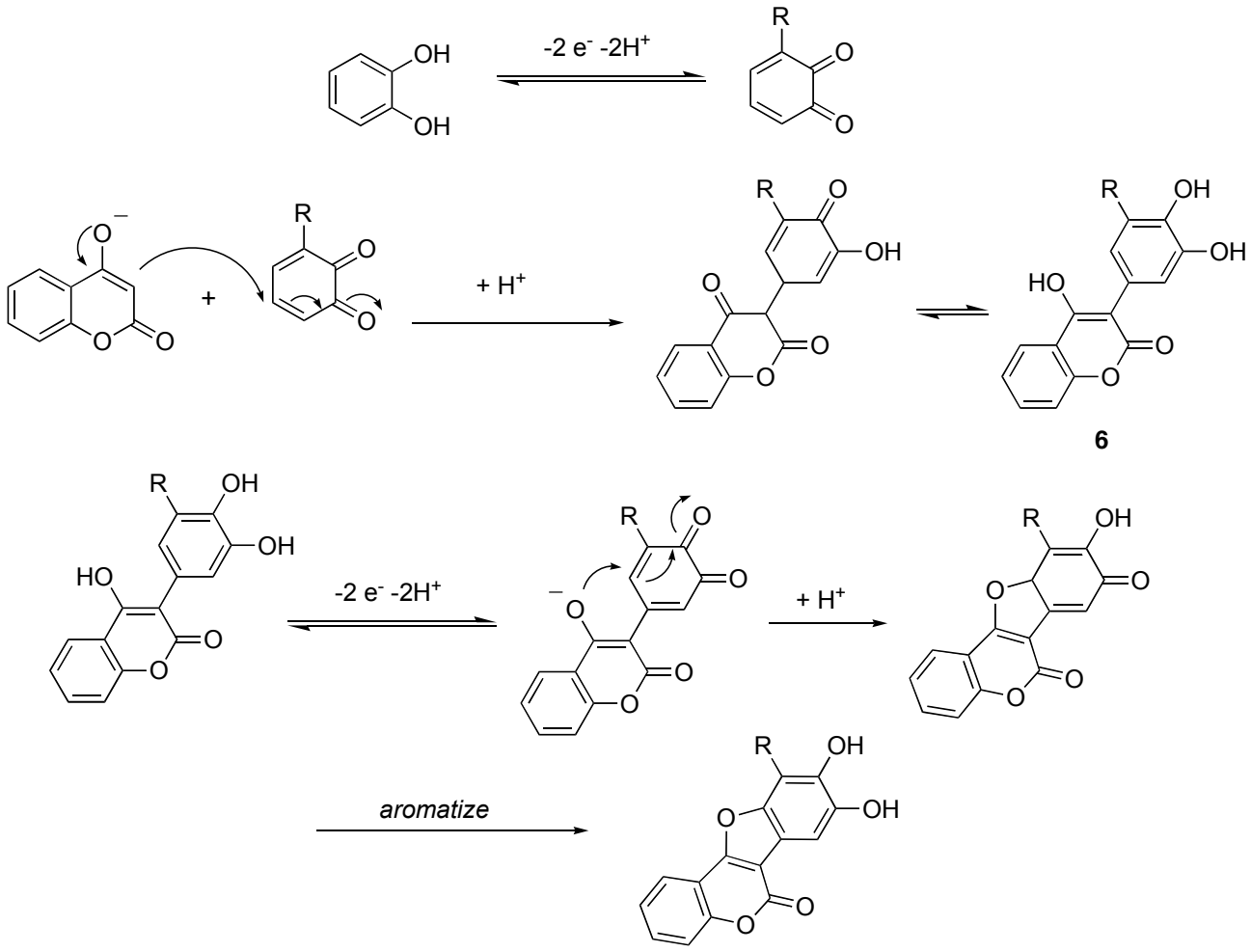


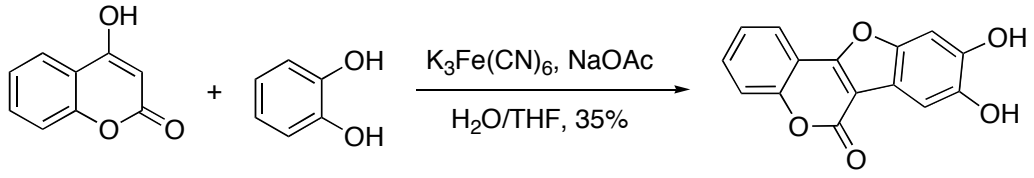
Figure 6. Wanzlick's synthesis of coumarone derivatives

The proposed mechanism for accessing these scaffolds, shown in **Scheme 2**, begins with the oxidation of catechol to the *o*-quinone. Michael addition of the nucleophile into the *o*-quinone followed by aromatization generates the intermediate species **6**. A second oxidation to the *o*-quinone allows for ring closure to form the 5-membered ring and aromatization gives the desired furanosteroid.



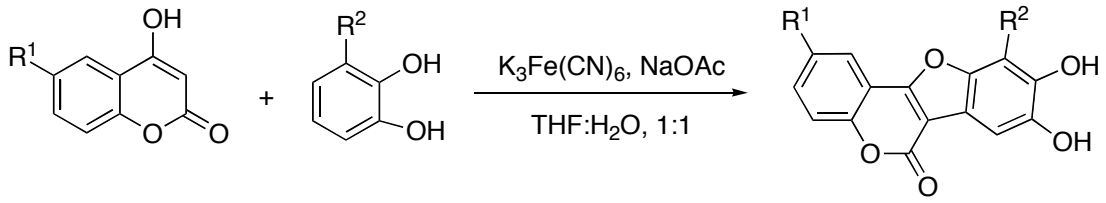
Scheme 2. Mechanism for the intermolecular cyclization reaction

For our synthesis, a solution of catechol **(4)**, 4-hydroxycoumarin **(3)**, and NaOAc in water/THF was treated with $K_3Fe(CN)_6$ to provide the resultant furanosteroid **5 (JLV1001)** in 35% yield **(Scheme 3)**. Using this $K_3Fe(CN)_6$ protocol, five additional library members were synthesized from a selection of commercially available catechols and 4-hydroxycoumarins **(Scheme 4)**.[30,32]



3 **4** **5**

Scheme 3. Intermolecular condensation using $K_3Fe(CN)_6$



JLV1009 (7) R^1= H, R^2= OMe; 31%
JLV1052 (8) R^1= H, R^2= Me; 18%
JLV1055 (9) R^1= Me, R^2= H; 25%
JLV1061 (10) R^1= Me, R^2= Me; 30%
JLV1066 (11) R^1= Me, R^2= OMe; 15%

Scheme 4. Synthesis under potassium ferricyanide conditions

The products were isolated via filtration or extraction and purified via recrystallization. In all cases, the product was obtained as a single regioisomer and the structures were confirmed by HMBC 2-D NMR experiments **(Figure 7)**.

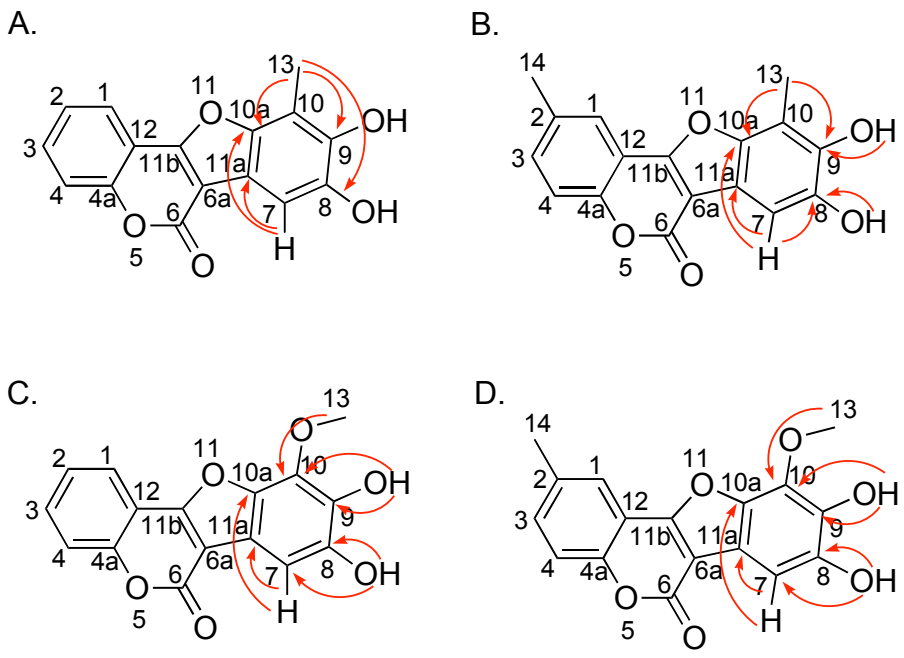
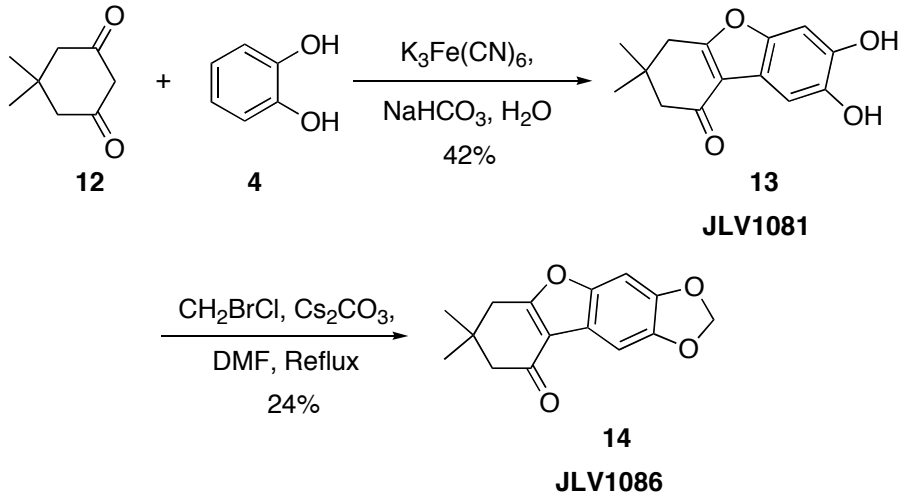


Figure 7. Relevant HMBC correlations for synthetic analogs

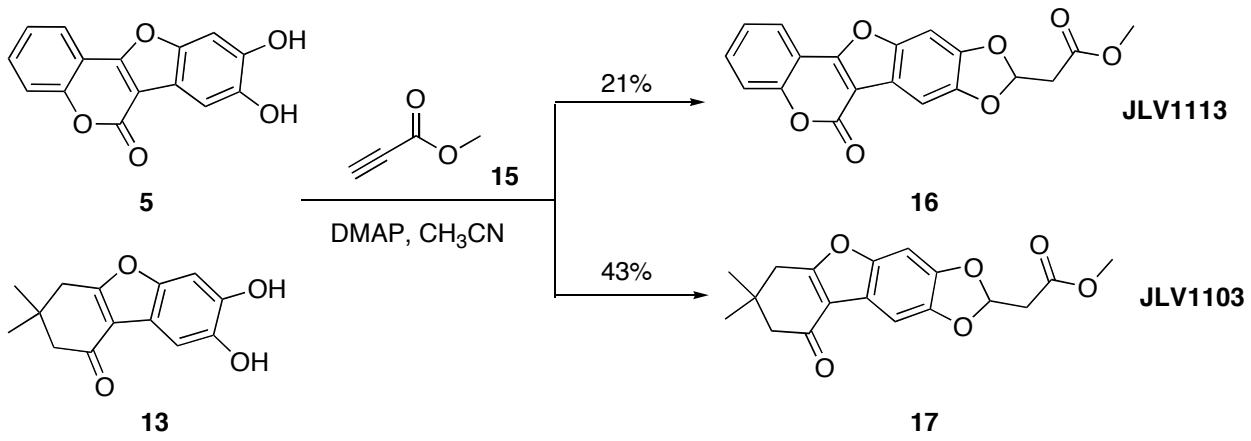
According to the HMBC spectral data for entry **JLV1052 (8)**, the H-13 methyl protons correlated to the hydroxyl containing carbons, C-9 and C-8, as well as furan carbon C-10a but not the C-11a furan carbon. The H-7 proton showed cross peaks with both of the hydroxyl containing carbons C-9 and C-8, as expected. A correlation between H-7 and C-10a was apparent as well as a correlation between H-7 and the C-11a carbon of the furan ring. These are consistent with the proposed structure for **JLV1052 (8)**. The structures for **JLV1009 (7)**, **JLV1061 (10)**, and **JLV1066 (11)** were determined in an analogous fashion where the H-7 proton showed a correlation with the C-11a quaternary carbon at the furan ring junction. In support of these analyses, the ^{1}H and ^{13}C NMR data for analog **JLV1066 (11)** were an exact match for the known compound.[39]

Two additional library members were accessed using Wanzlick's literature protocol[46,47] in which dimedone **(12)** and catechol **(4)** were treated with $NaHCO_3$ and $K_3Fe(CN)_6$ in water, generating the requisite benzofuran **13 (JLV1081)** in 42% yield **(Scheme 5)**. The catechol moiety of the benzofuran was subsequently converted to the formylidene acetal with CH_2BrCl and Cs_2CO_3 to give **14 (JLV1086)** in 24% yield.



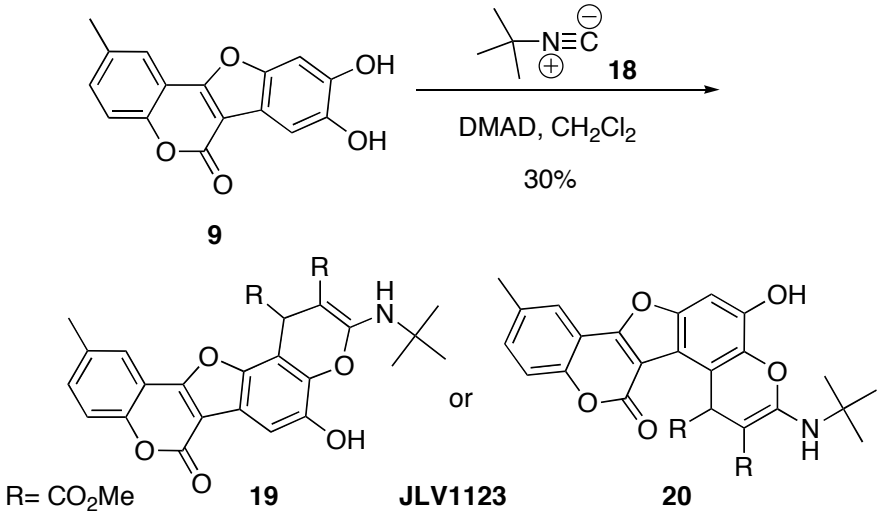
Scheme 5. Condensation reaction and subsequent formylidene formation

Side chain diversification in this series was achieved via the acetalization of the catechol moiety as the 2-ethylidene ester **(Scheme 6)**. Compounds **5** (**JLV1001**) and **13 (JLV1081)** were treated with methylpropynoate **(15)** and DMAP in CH_3CN to afford compounds **16** (**JLV1113**) and **17 (JLV1103)** in 21% and 43% yield, respectively.[48]



Scheme 6. Acetalization of catechol moiety of compounds 5 and 13

Additionally, we found that we could enhance structural complexity via an E-ring annulation of **9 (JLV1055)** with DMAD and *t*-butyl isocyanide **(18).**[49,50] This process gave rise to one of two potential regioisomers depicted in **Scheme 7.** Analysis of the HMQC and HMBC spectra **(Figure 8)** showed that the three relevant protons (shown in green) had a 4-bond correlation with a common carbon, C_{6a}. Compound **19** has one of the relevant protons is four bonds away from the common carbon; however, the other two relevant protons are three bonds and five bonds away from the C_{6a} carbon (shown with blue arrows). In compound **20,** the three differentiating protons (shown in green) have a 4-bond correlation with one common carbon, C_{6a}. Thus, the HMBC data supports the structure for regioisomer **20**. Initially, we thought that compound **19** would be the major product due to how sterically crowded compound **20** seems to be between the methylester and the lactone carbonyl. Perhaps due to the rigid planar nature of this steroid-type system those interactions do not hamper the formation of this compound as the exclusive product.



Scheme 7. Potential products from E-ring annulation via a multicomponent reaction manifold

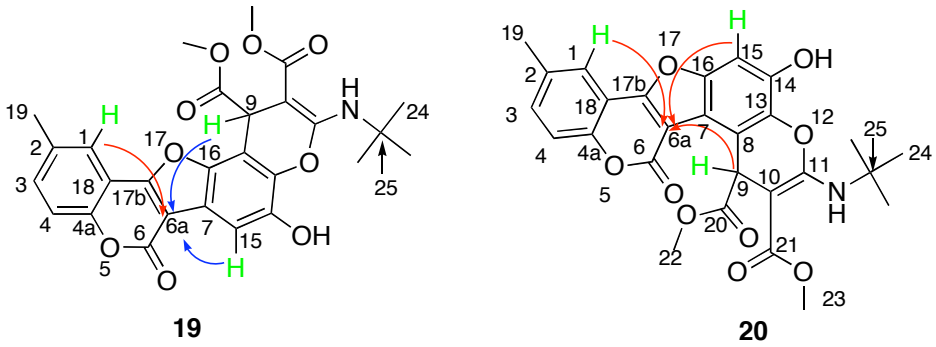


Figure 8. Analysis of relevant HMBC correlations for JLV1123

1.3 BIOLOGICAL RESULTS FOR PI3-KINASE INHIBITORS

A library totaling 18 compounds comprised of 11 synthetic furanosteroid analogs (**Figure 9)** and 7 commercially available compounds purchased from Sigma-Aldrich, Acros, and TIM-TEC (**Figure 10)** was submitted to Dr. Garth Powis, the director of the Center for Targeted Therapy at the University of Texas M. D. Anderson Cancer Center and tested as inhibitors against PI3-kinase Ia p110 alpha.

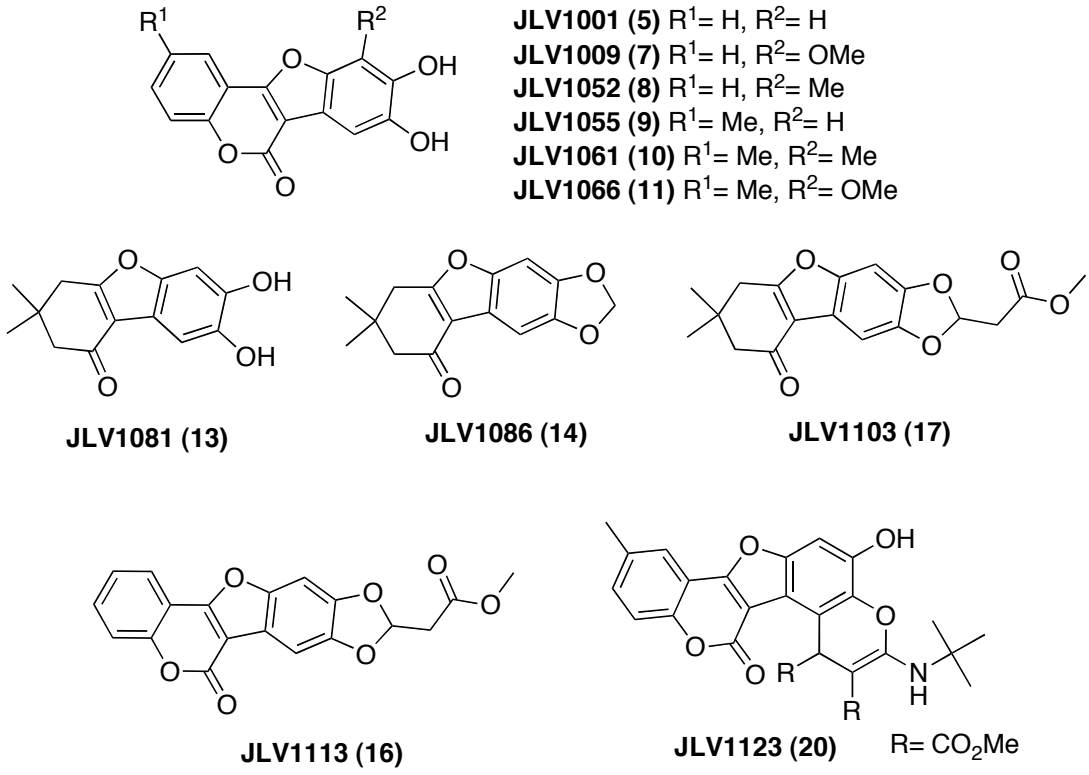


Figure 9. Furanosteroid analogs tested for PI3K inhibition

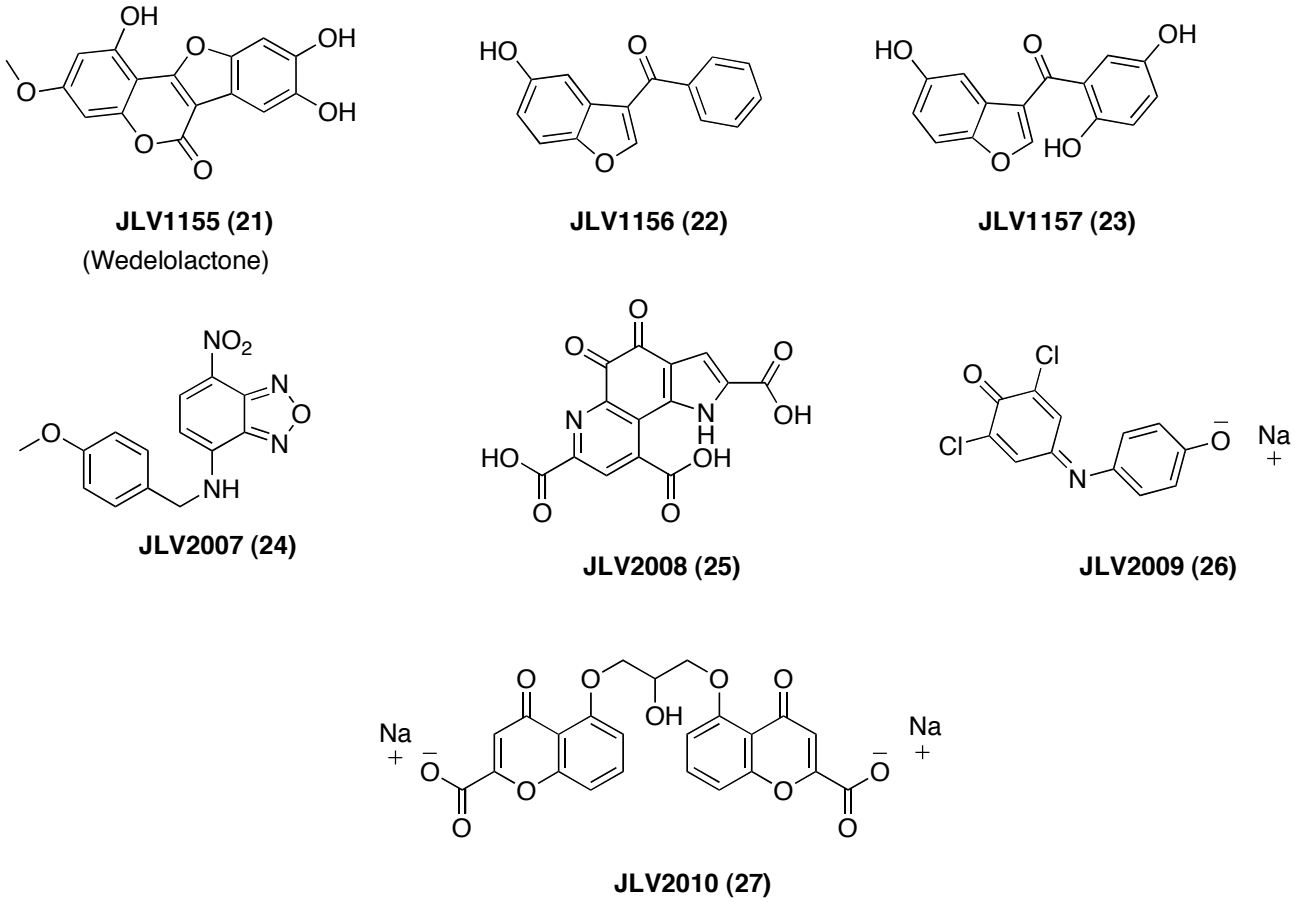


Figure 10. Commercial compounds tested for PI3K inhibition

The Powis group conducted a competitive assay with ATP against the active p110alpha/p85alpha PI3K using an ELISA colorimetric assay. Essentially, PtdIns-P_2, ATP, the active enzyme and the compound of interest were added to a buffered solution and the conversion of PtdIns-P_2 to PtdIns-P_3 was measured. The control for this assay was wortmannin, which was evaluated at 1 nM and 10 nM final concentrations in DMSO.

An initial diagnostic screen of the compounds against PI3-K p110 alpha was conducted and the results are summarized in **Table 3**. Compounds **JLV1009 (7)**, **JLV1052 (8)**, **JLV1081 (13)**, **JLV1103 (17)**, **JLV1113 (16)**, **JLV1123 (20)**, **JLV1156 (22)**, and **JLV1157 (23)** were not active, all possessing IC_{50} values greater than 1 μM. The IC_{50} for compounds **JLV1001 (5)**, **JLV1055 (9)**, **JLV1061 (10)**, **JLV1066 (11)**, **JLV1086 (14)**, and **JLV1155 (21)** were in the 0.01 μM range.

Table 3. Biological results against PI3K

Compound	Compound ID	PI3-K p110 alpha IC_{50} (μM)
5	**JLV1001**	≥ 1.0
7	**JLV1009**	< 1.0
8	**JLV1052**	< 1.0
9	**JLV1055**	> 0.01
10	**JLV1061**	> 0.01
11	**JLV1066**	≥ 0.01
13	**JLV1081**	< 1.0
14	**JLV1086**	≥ 0.01
16	**JLV1113**	< 1.0
17	**JLV1103**	< 1.0
20	**JLV1123**	< 1.0
21	**JLV1155**	≥ 0.01
22	**JLV1156**	< 1.0
23	**JLV1157**	< 1.0

The compounds were initially assayed against the active enzyme p110 alpha in two batches and their percent inhibition was measured at 0.0001, 0.001, 0.01, 0.1, and 1 µM **(Figure 11)**. In the first batch, compounds **JLV1009 (7)**, **JLV1052 (8)**, **JLV1081 (13)** were the least potent inhibitors, producing no more than a 30% inhibition of enzyme activity at 0.01 µM. Compounds **JLV1055 (9)** and **JLV1001 (5)** were more potent causing a decrease in enzyme activity within the 48-55% range at 0.01 µM. The most promising compound for this first batch was **JLV1061 (10)**, which reduced the activity of the enzyme to 43% at 0.01 µM.

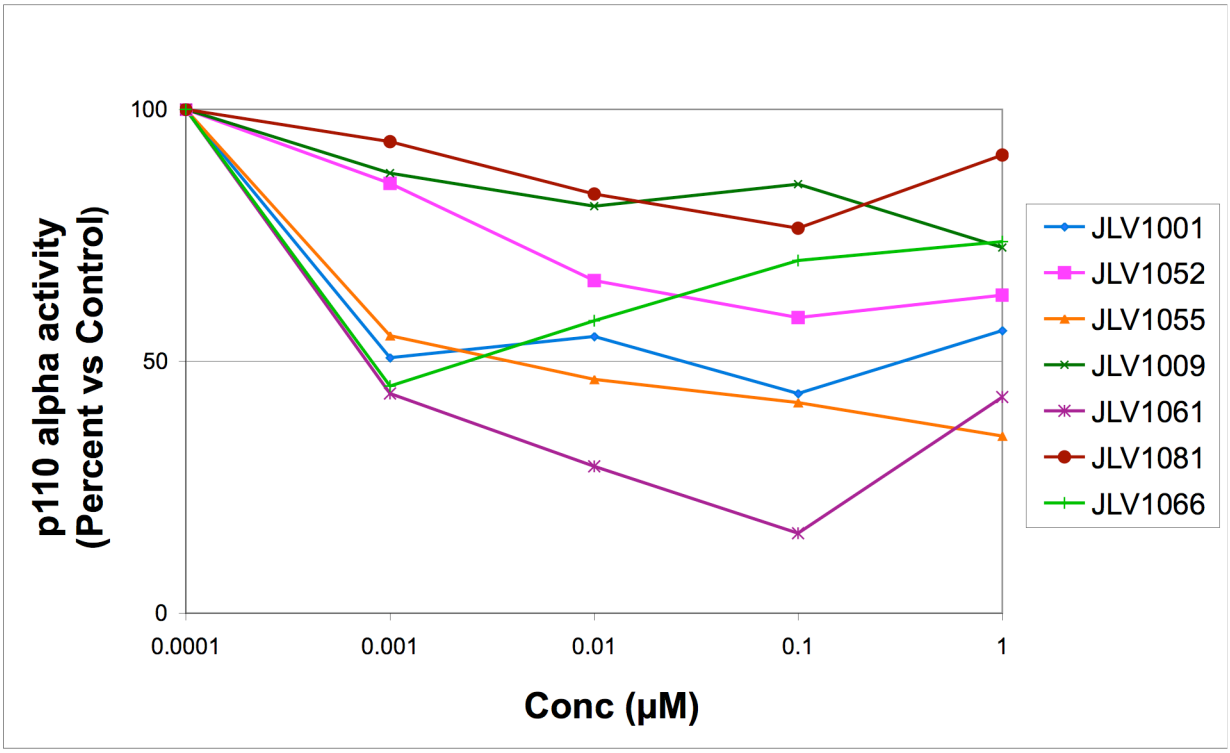


Figure 11. JLV compound activity against p110 alpha (batch 1)

In the second batch, none of the compounds inhibited the enzyme below 60% at 0.001 µM **(Figure 12)**. Compounds **JLV1155 (21)** and **JLV1156 (22)** were the best inhibitors at 0.01 µM, where both reduced activity to 52% and 55%, respectively. At 1 µM, **JLV1086 (14)** and **JLV1155 (21)** reduced the enzyme activity to 47% and 45%, respectively.

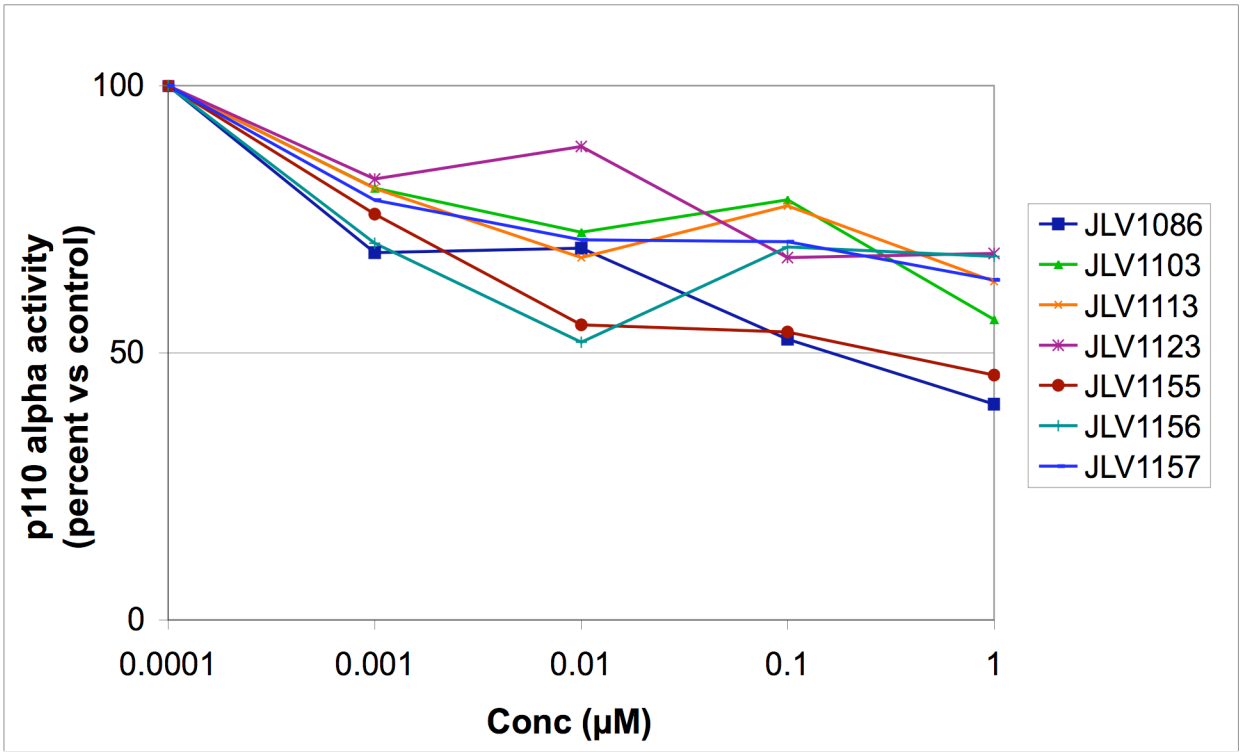


Figure 12. JLV compound activity against p110 alpha (batch 2)

The compounds exhibiting moderately potent IC_{50} values determined by the initial diagnostic screen were analyzed further in a second series of assays against p110 alpha and p110 delta. In the assay against p110 alpha the compounds were evaluated at 0.01, 0.1 and 1.0 µM. All of the compounds inhibited the active enzyme only to about 50% activity with the exception of **JLV1155 (21),** which demonstrated about 75% inhibition of the active enzyme **(Figure 13)**. Interestingly, **JLV2010 (27)** showed promising inhibitory effects at 1 µM, producing a decrease in enzyme activity to below 20%.

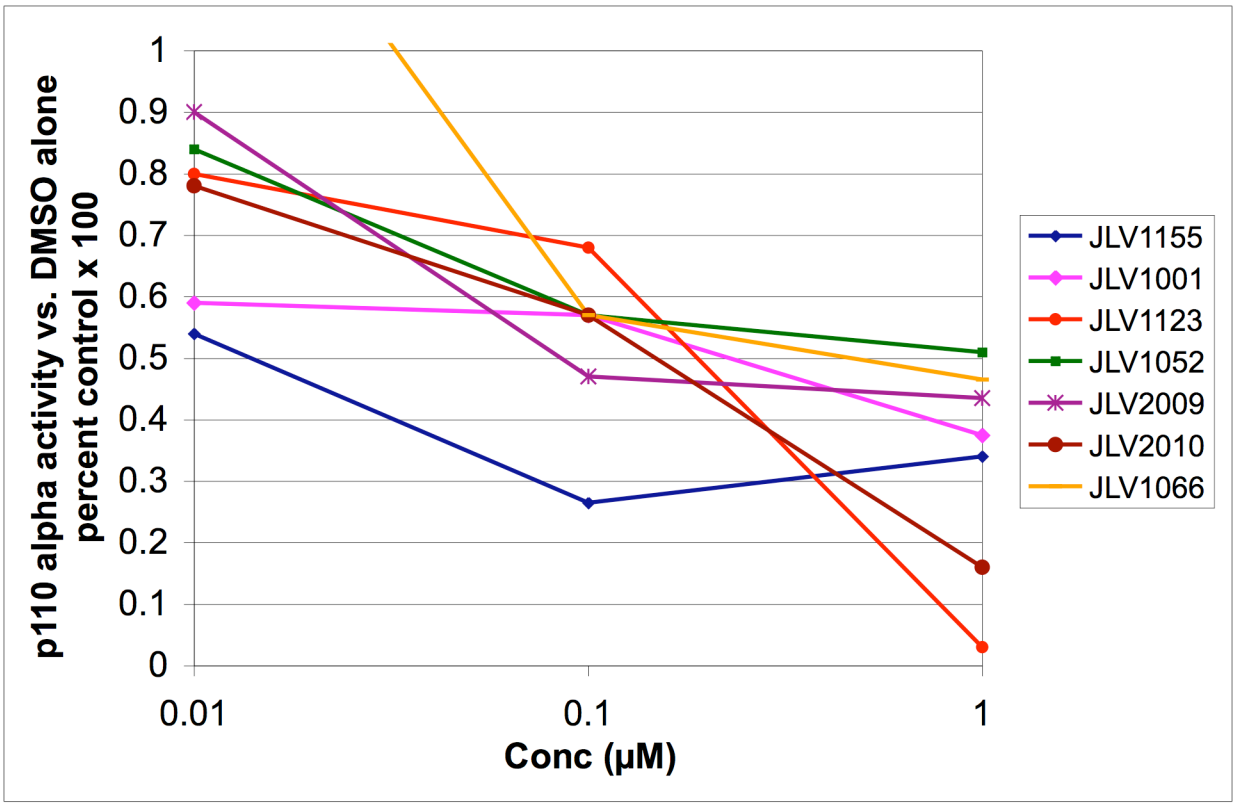


Figure 13. JLV compound activity against p110 alpha

Compounds **JLV1001 (5)**, **JLV1155 (21)**, **JLV2010 (27)**, and **JLV1052 (8)** were assayed against p110 delta and evaluated at 0.01, 0.1 and 1 µM **(Figure 14)**. Compound **JLV1155 (21)** was the most potent inhibitor in this case with a percent inhibition of 75% at 0.1 µM. Compound **JLV1052 (8)** exhibited a 40% inhibition of the active enzyme at 0.1 µM and compounds **JLV2010 (27)** and **JLV1001 (5)** showed a 20% inhibition or less.

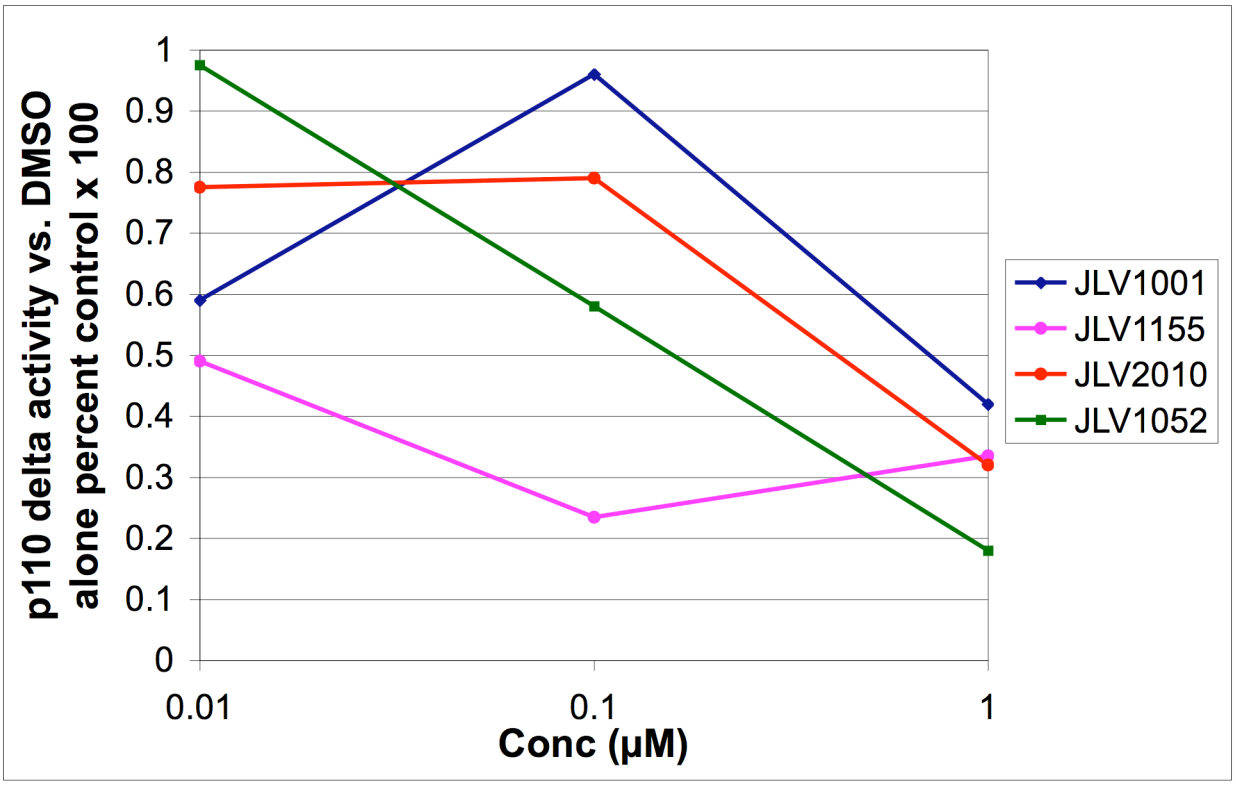


Figure 14. JLV compound activity against p110 delta

With compound **JLV1155 (21)** being the most promising hit from these assays we wanted to evaluate its inhibitory effects in tumor cells. Using the human lung adenocarcinoma epithelial cell line A549 and the breast cancer cell line MCF-7, **JLV1155 (21)** was tested at both 1 μM and 10 μM and the effects were observed after 0, 16, and 24 h time points **(Figure 15)**. For both cell lines, there was no inhibition observed even after 24 h.

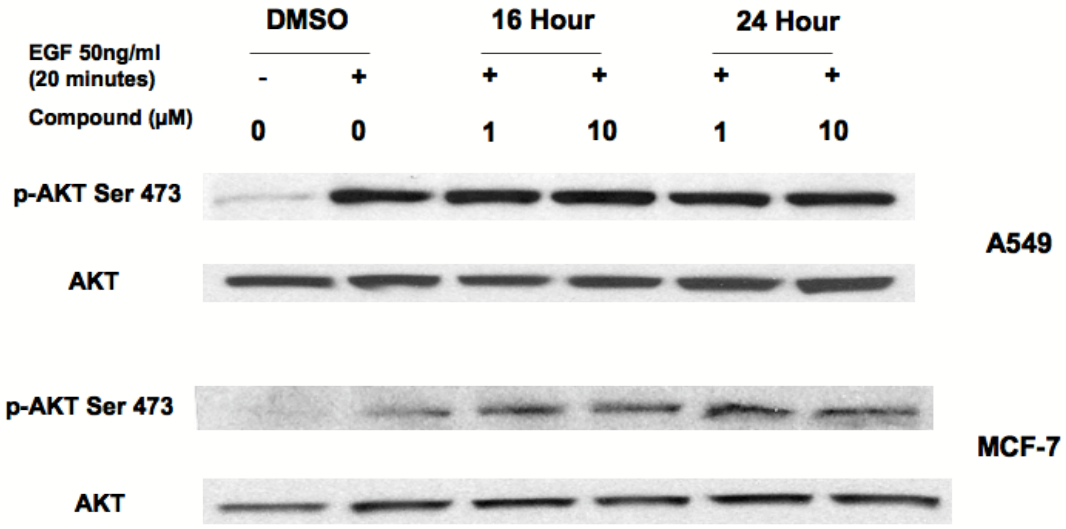


Figure 15. Biological results for JLV1155 (21) against A549 and MCF-7 cell lines

1.3.1 Conclusions and acknowledgements

A library of furanosteriod derivatives was synthesized by an iron mediated condensation reaction of a catechol and a 4-hydroxycoumarin. The resultant furanosteroids were analyzed by 2D-NMR HMBC experiments to confirm the regiochemical outcome of the reactions. These compounds were diversified by acetalization of the catechol moiety and E-ring annulation via a multicomponent cyclization. These compounds along with 7 structurally related samples obtained from commercial sources were tested for their inhibitory activity against PI3K p110alpha/p85alpha. The compounds were analyzed via a competitive ELISA colorimetric assay. Each series of compounds were assayed at 0.01, 0.1, and 1.0 μM against the control, wortmannin in DMSO. **JLV1155 (21)** was the most potent inhibitor against p110 alpha and p110 delta, with a 75% inhibition of both enzymes at 0.1 μM. With these promising results, we tested **JLV1155** against A549 and MCF-7 tumor cell lines, both widely accepted as model cell lines for evaluating biological effects of potential inhibitors. Previous studies have shown that wortmannin is a potent inhibitor of PI3K in both cell types, thus making these cell lines suitable for preliminary biological assays.[2,7] However, despite its potency in our competitive assay, when A549 and MCF-7 cancer cells were treated with this compound, there was no observed inhibitory effect. Based on the data from these assays there is no evidence that these compounds are binding to the ATP-binding site of the p110 domain of the active enzyme.

We would like to thank Dr. Garth Powis and Nathan Ihle from the Center of Targeted Therapy for providing the biological assay data discussed in this chapter including graphs, charts, and figures.

1.4 CROMOLYN BASED INHIBITORS

In our initial library of potential PI3-kinase inhibitors, the commercially available disodium cromoglycate **(JLV2010, 27)** exhibited an 85% inhibition of active enzyme PI3K-p110 alpha **(Figure 13)** and a 70% inhibition against PI3K-p110 delta at 1.0 μM **(Figure 14).** With these findings, we wanted to develop the SAR of this compound through the synthesis of several structural analogs.

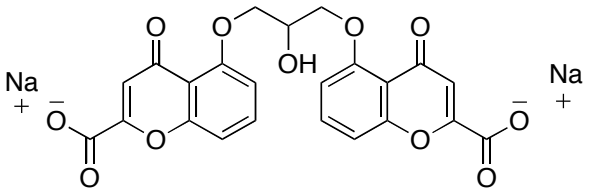


Figure 16. Disodium cromoglycate (DSCG, 27)

In the 1960's, cromolyn or disodium cromoglycate (DSCG) **(Figure 16)** was introduced as a clinical treatment for allergic diseases including asthma, rhinitis and conjunctivitis.[51] The postulated mode of action of DSCG is related to its stabilizing effect on the mast cell membrane, preventing the release of the mediators of anaphylaxis, the exaggerated allergic reaction to a foreign protein resulting from previous exposure to the agent.[52] Conventionally, anti-allergic activity has been measured by the ability of compounds to stabilize rat skin connective tissue mast cells (PCA test) or inhibit antigen-induced mediator release from passively sensitized human lung fragments.[51,53] Since its discovery, however, researchers and clinicians now

recognize that asthma is a multicomponent disease and the therapeutic usefulness of DSCG is a result of more than one mode of action.[51]

DSCG **(27)** is highly polar and has a low lipophilicity, which leads to its poor absorption in the gastrointestinal tract and rapid elimination from the body.[51,52,54] As a result, DSCG is only an effective treatment for asthma if administered via inhalation. Although attempts to produce an orally effective anti-allergic agent have met with difficulty, recently the benefits of inhalation therapy have been recognized, and this method for administration is now widely preferred therapeutically for the treatment of asthma.[51]

Although DSCG has been recognized as a leading treatment for allergic disease, to our knowledge this structural motif has not been studied as a potential inhibitor of the PI3-kinase pathway.

1.4.1 Synthesis of cromolyn analogs

The previously reported syntheses of cromolyn structural analogs have focused on derivatizing three major reactive sites: the carboxyl, hydroxyl, and keto functionalities **(Figure 17)**.[52] Studies have also been conducted varying the type, length, and connectivity of the linker between the two chromene moieties **(Figure 18)**.[55]

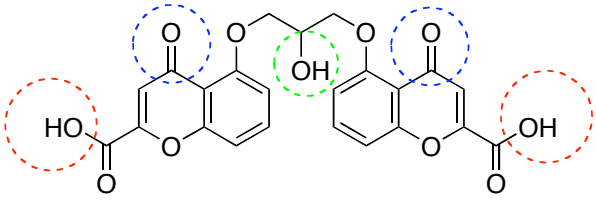


Figure 17. Three main sites of derivatization in cromolyn

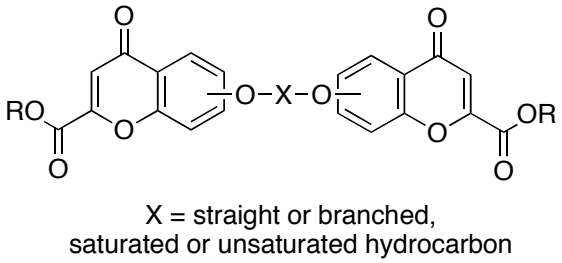


Figure 18. Cromolyn derivatives with varying linker

The focus of our synthesis of cromolyn analogs was to derivatize the parent structure in two areas: first by adding an additional substitution on the 2-hydroxypropane linker (R^1) and secondly adding additional substitution on the chromene ring system (R^2) **(Figure 19)**.

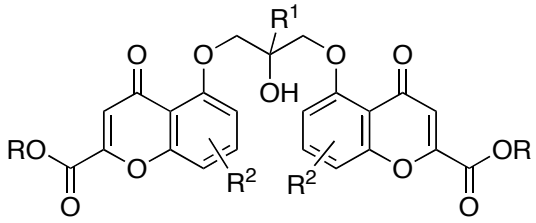
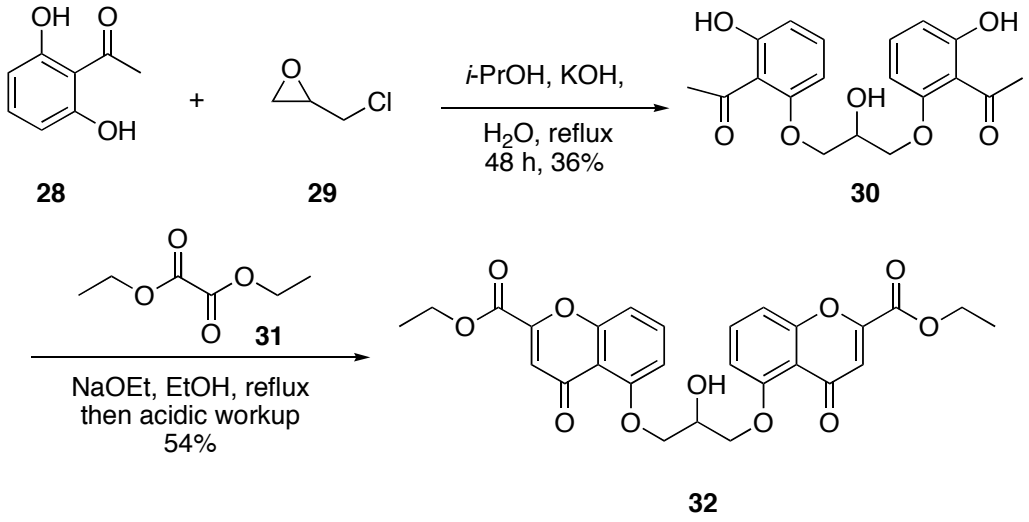


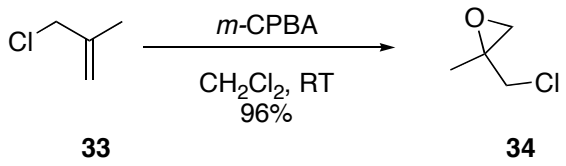
Figure 19. General substitution pattern for cromolyn analogs

For our synthesis of cromolyn analogs, 2',6'-dihydroxyacetophenone **28** and epichlorohydrin **(29)** were heated at reflux in KOH and *i*-PrOH to give the bis-acetophenone (**30)** in 36% yield **(Scheme 8)**. Treating compound **30** with diethyl oxalate **(31)** in sodium ethoxide/ethanol at reflux generated the desired bis-ester in 54% yield.[54,55]



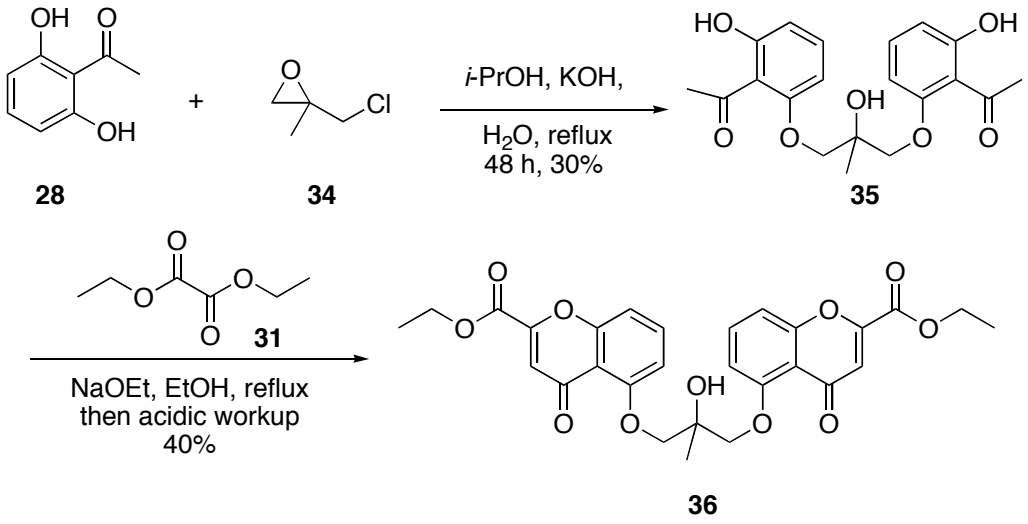
Scheme 8. Synthesis of diethyl 5,5'-(2-hydroxypropane-1,3-diyl)bis(oxy)bis(4-oxo-4H-chromene-2-carboxylate)

Cromolyn derivatives could be synthesized using 2-substituted epichlorohydrin derivatives instead of commercially available epichlorohydrins. To that end, 2-methyl epichlorohydrin **(34)** was synthesized via epoxidation of 3-chloro-2-methylprop-1-ene **(33)** with *m*-CPBA in CH_2Cl_2 in 96% yield **(Scheme 9)**.[56]



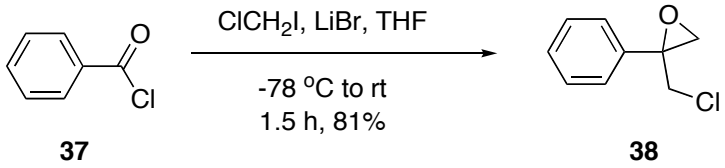
Scheme 9. Synthesis of 2-(chloromethyl)-2-methyloxirane (34)

The resulting epichlorohydrin derivative **34** and 2',6'-dihydroxyacetophenone **(28)** were treated with KOH in *i*-PrOH at reflux to generate bis-acetophenone **35** in 30% yield **(Scheme 10)**. Subsequent condensation with diethyl oxalate **(31)** in sodium ethoxide/ethanol at reflux generated the desired bis-ester **36** in 40% yield.



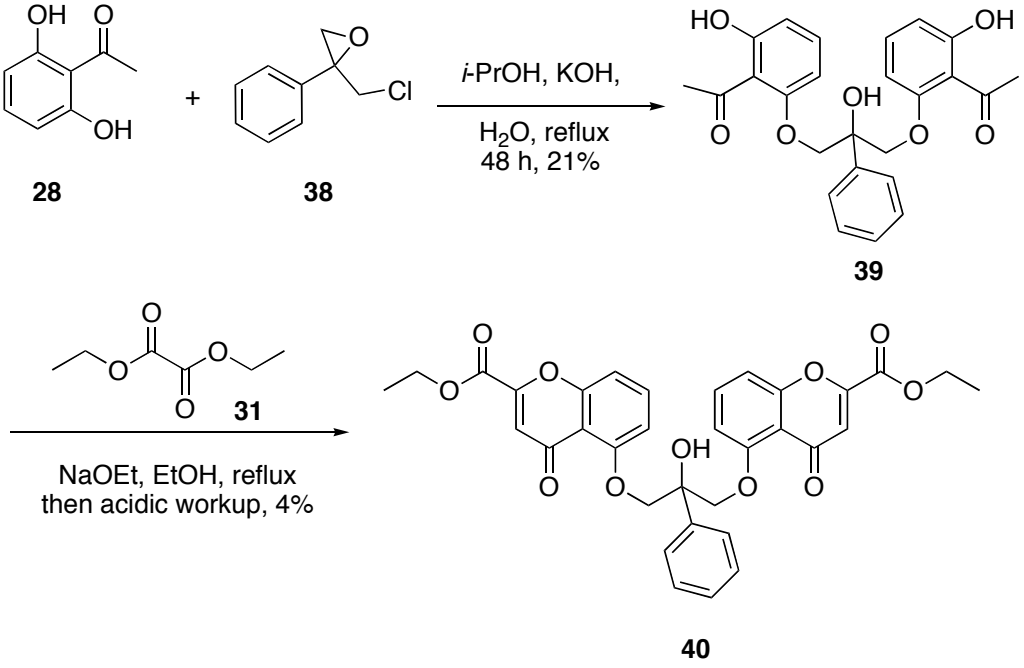
Scheme 10. Synthesis of diethyl 5,5'-(2-hydroxy-2-methylpropane-1,3-diyl)bis(oxy)bis(4-oxo-4H-chromene-2-carboxylate) (36).

The synthesis of 2-(chloromethyl)-2-phenyloxirane **(38)** was achieved via the treatment of acid chloride **37** with chloroiodomethane and lithium bromide in THF **(Scheme 11)**.[57] Upon distillation of the crude reaction mixture, the desired epoxide **38** was obtained in 81% yield.



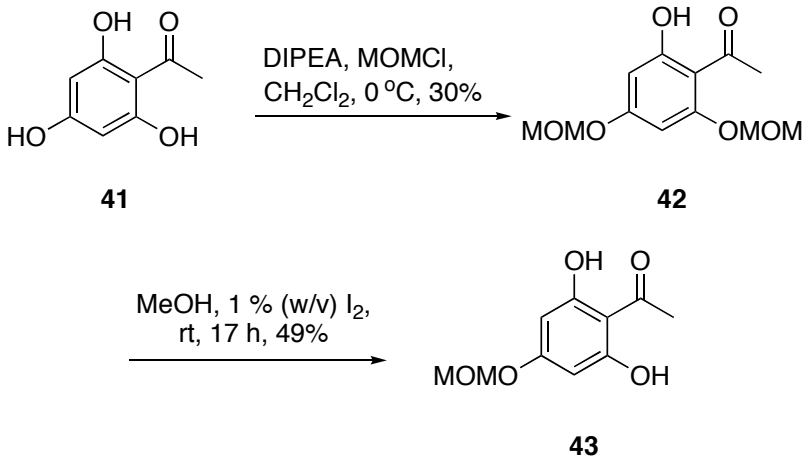
Scheme 11. Synthesis of 2-(chloromethyl)-2-phenyloxirane (37)

Epoxide **38** and 2',6'-dihydroxyacetophenone **(28)** were heated at reflux in KOH and *i*-PrOH for 48 h to afford compound **39** in 21% yield **(Scheme 12)**. Treatment of **39** with diethyl oxalate **(31)** in refluxing sodium ethoxide/ethanol generated the desired bis-ester **40** in low 4% yield, which can be attributed to mass loss during the difficult purification of the product from the reaction mixture. The ^{1}H NMR for the crude ester **40** was significantly messier than that of the methyl analog **36.** After an initial purification by column chromatography on silica gel, significant impurities were still present which made multiple purifications necessary.



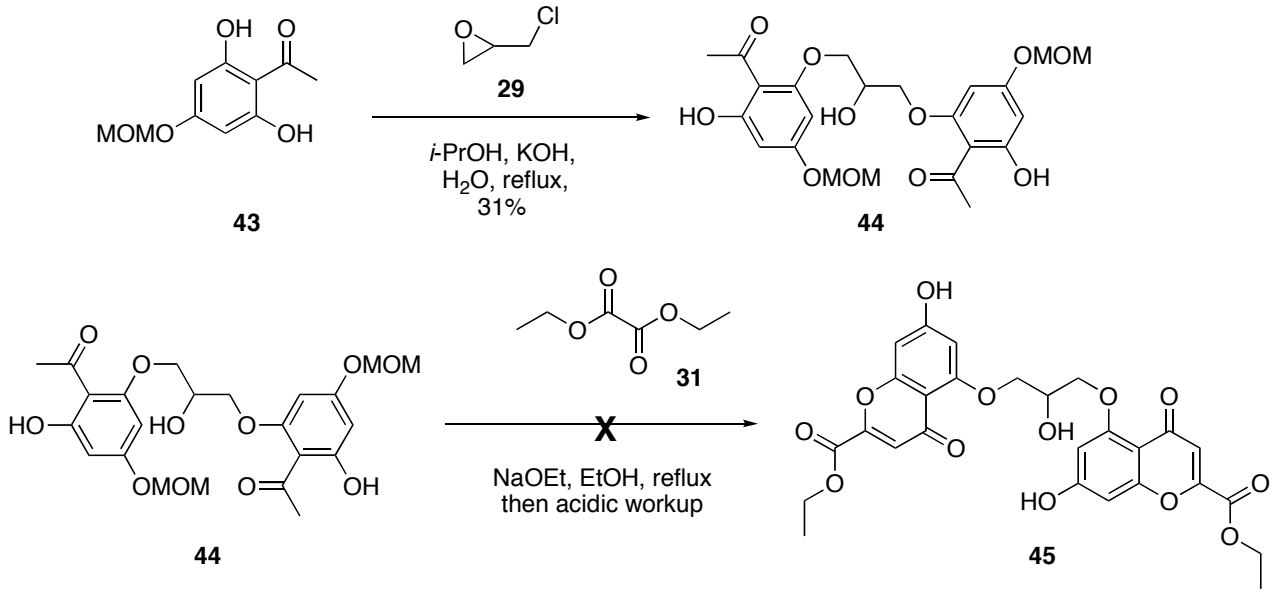
Scheme 12. Synthesis of diethyl 5,5'-(2-hydroxy-2-phenylpropane-1,3-diyl)bis(oxy)bis(4-oxo-4H-chromene-2-carboxylate) (40)

In order to access different substitutions on the chromene core, 2,4,6-trihydroxyacetophenone **(41)** was selectively protected as MOM-ether **43** via a two-step protocol **(Scheme 13)**.[58-60] Compound **41** was treated with DIPEA and MOMCl solution[61] in CH_2Cl_2 to afford the 4,6-bis-MOM-ether **42** in 30% yield. Compound **42** was subsequently treated with 1% (w/v) I_2 in MeOH to selectively deprotect the *ortho*-MOM ether function and furnish the mono-MOM-ether **43** in 49% yield.



Scheme 13. Synthesis of 1-(2,6-dihydroxy-4-(methoxymethoxy)phenyl)ethanone

Compound **43** was treated with KOH and epichlorohydrin **(29)** and heated at reflux in *i*-PrOH for 48 h to give the desired bis-acetophenone **44** in 31% yield **(Scheme 14)**. When compound **44** was treated with diethyl oxalate **(31)** in sodium ethoxide/ethanol at reflux, the desired bis-ester **45** was not observed. Analysis of the crude ^{1}H NMR spectrum revealed that the MOM-ethers had been cleaved, perhaps during the acidic workup, and the product appeared to be a mixture of phenol containing compounds. The crude mixture did not contain the diagnostic α-proton of the α,β-unsaturated carbonyl group indicating that the condensation did not proceed. No further investigations to identify the compounds within this crude mixture were conducted.



Scheme 14. Synthetic approach toward diethyl 5,5'-(2-hydroxypropane-1,3-diyl)bis(oxy)bis(7-hydroxy-4-oxo-4H-chromene-2-carboxylate) (45)

In the event that the condensation reaction with compound **44** had proceeded as expected our synthetic plans to further derivatize ester **45** are highlighted in **Figure 20.** We recognized that we could access a variety of analogs through the conversion of the free phenols to a variety of alkyl-ethers (ie. benzyl, MOM, or PMB) and esters (ie. acetyl). Additionally, the analogous bis-acids could be obtained via saponification of the ethyl ester providing another avenue for derivatization.

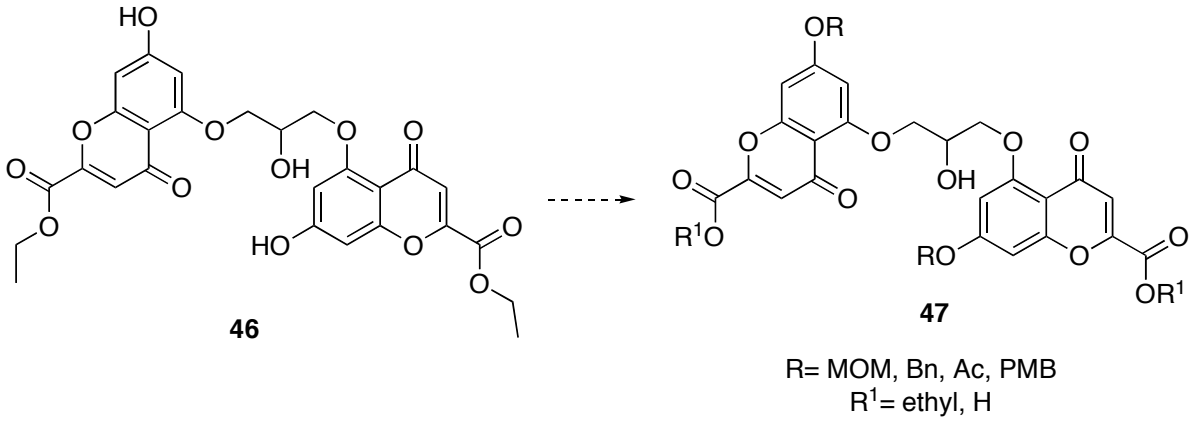


Figure 20. Synthetic plan for additional cromolyn derivatives

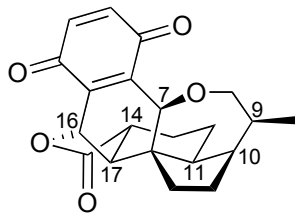
1.5 CONCLUSIONS

In our initial biological investigations for PI3K inhibitors, compound **JLV2010 (27,** DSCG) was found to be the most potent at 1.0 μM concentration. A subset of analogs of **27** was synthesized via a two-step protocol. 2'6'-dihydroxyacetophenone was first dimerized with the 2-methyl and 2-phenyl epichlorohydrin derivatives to form the requisite bis-phenol compounds. These substrates were subsequently condensed with diethyl oxalate to provide the desired bis-chromone compounds. Attempts to introduce additional substitution on the chromene ring were unsuccessful. Biological investigations of these derivatives as potential PI3-kinase inhibitors will be explored in future assays.

2.0 STUDIES TOWARD THE TOTAL SYNTHESIS OF PLEUROTIN

2.1 INTRODUCTION

Pleurotin (**48)**, first isolated in 1947, is a fungal metabolite found in extracts of *pleurota griseus*, as well as *Hohenbruehelia geogenius* and *Hohenbruhelia atrocaerulea* **(Figure 21)**. The structure was assigned by degradative studies[62] in 1968, and later confirmed by x-ray crystallographic analysis.[63] Structurally, pleurotin is an interesting synthetic target containing a hexacyclic core with 8 stereocenters, 6 of which are contiguous. Also present is a quinone moiety that contains two benzylic leaving groups critical for its reactivity in biological systems.



48

Figure 21. Structure of pleurotin

2.1.1 Biology

Preliminary biological investigations demonstrated that pleurotin **(48)** was significantly active against gram-positive bacteria, such as *Staphylococcus aureus* (0.8 μg/mL), *Bacillus subtilis* (0.2 μg/mL), and *Bacillus mycoides* (1.6 μg/mL).[64] Further studies reported potent antitumor activity against Erlich ascites carcinoma, L1210 lymphoid leukemia, and mammary tumors.[64-66] Most interestingly, pleurotin has been identified as a potent inhibitor of the thioredoxin/thioredoxin reductase (Trx/TrxR) biological system.[29]

2.1.1.1 Thioredoxin/Thioredoxin Reductase (Trx/TrxR)

The thioredoxin reductases (TrxR) are low molecular weight flavoproteins that are widely expressed in prokaryotes and eukaryotes.[67] The thioredoxins (Trx), belonging to a family of pyridine nucleotide-disulphide oxidoreductases, are homodimeric. Each monomer is composed of an FAD prosthetic group, an NADPH binding site, and a conserved redox-active disulfide containing amino acid active site (-Trp-Cys-Gly-Pro-Cys-Lys-).[67-69] The reversible oxidation/reduction of the two cysteine (Cys) residues is essential for the biological activity of Trx. [69,70] Initially the Trx/TrxR system was studied in E. Coli[71] with the conserved amino acid active site containing normal Cys residues.[71] Later, it was discovered that the human thioredoxin active site differs from the bacterial Trx active site in that the Cys residues are replaced by selenocysteine (Sec) residues.[67] The mammalian Trx/TrxR are expressed as isoforms localized in the cytosol (TrxR1, Trx1) and mitochondria (TrxR2, Trx2).[67,72,73] TrxR1 is known for its potent and distinct immunomodulatory functions and TrxR2 is known for protecting against oxidative stress.[67] The third isoform, TrxR3, is primarily expressed in the testis. In contrast to the other isoform, TrxR3 can reduce glutathione disulfide in addition to Trx, thus leading to the name,

TGR, for its thioredoxin/glutathione reductase activity.[67,72,73] All three of the mammalian Trx isoforms are selenoproteins whose disulfide reduction activity involves a flexible active site located at the carboxy-terminus, making it easily accessible for both selective and irreversible modification by electrophiles.

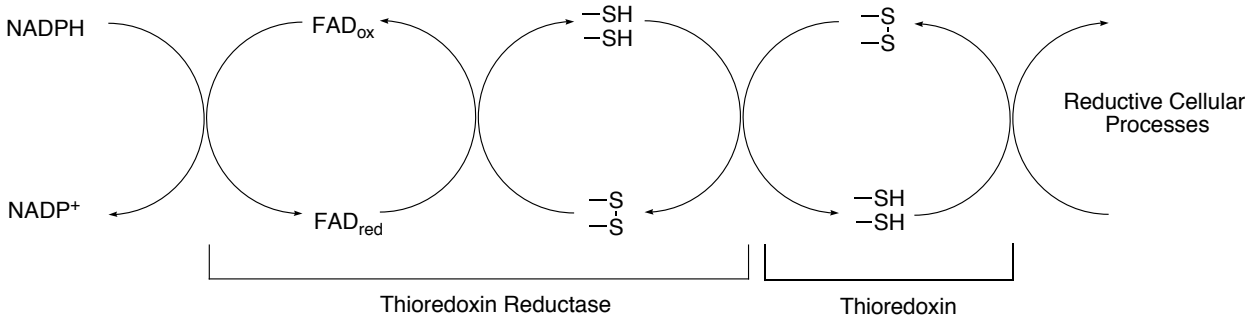


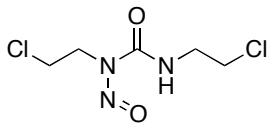
Figure 22. Mechanism for Trx/TrxR system in E. Coli

The mechanism of action for the Trx/TrxR system involves the transfer of electrons from NADPH by way of FAD to the active site disulfide of TrxR, which then goes on to reduce the substrate Trx (**Figure 22**).[72] The Trx enzyme participates in various reductive cellular processes such as the reduction of Trx peroxidase for the conversion of hydrogen peroxide into water, as well as the conversion of ribonucleotides to deoxyribonucleotides for DNA synthesis.[72] Trx also modulates transcription factor activities leading to increased binding to DNA and altered gene transcription. Studies have shown that Trx increases cell growth and also inhibits apoptosis.[72,74] TrxR1 is essential for maintaining redox homeostasis and protecting against oxidative damage and mutation in normal cells, however upon transformation into malignant cells TrxR1 supports tumor growth and progression.[75] In general, Trx protein levels are elevated in several human primary cancers with significant correlations between increased Trx levels, tumor proliferation, and inhibited apoptosis. [29,74,76]

The diverse range of biological functions of TrxR1 involved in the development and progression of cancer suggests that inhibiting Trx/TrxR is an ideal target for antitumor therapies. The objective of Trx targeting often involves the potential conversion from an antioxidant into a pro-oxidant Trx species *in vitro* and *in vivo*.[75] Many tumor cells possessing increased TrxR levels also display a significant resistance to chemotherapy, thus inhibition of Trx could aid in preventing or reversing resistance mechanisms.[75] Evidence has also shown that TrxR expression correlates with apoptotic resistance in various cancers.[69,74,77]

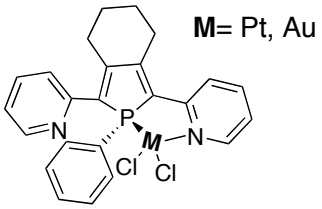
A selection of known Trx/TrxR inhibitors, highlighted in **Figure 23**, demonstrate the structural diversity among the various known agents for the inhibition of Trx/TrxR. The nitrosoureas, such as bis-chloroethyl-nitrosurea (BCNU) **49**, are non-selective alkylating agents that inhibit NADPH-reduced TrxR and GR.[75] Their ability to cross the blood-brain barrier makes them promising treatments against malignant gliomas, such as glioblastoma. Both Au and Pt-phospholes **50** have been developed as potent antiglioma agents via inhibition of TrxR *in vitro*.[75] The curcumin flavinoids **51**, representing naturally occurring polyphenol compounds, have been identified as efficient and oxidative stress-inducing inhibitors of mammalian TrxR in vitro with potential antitumor activity in various human cancer cell lines.[75,78] Auranofin **52**, a gold (I) thiosugar known for its activity against lymphocyte leukemia P338,[79] has been found to induce production of mitochondrial hydrogen peroxide at submicromolar concentrations related to TrxR inhibition.[75,80-82] Earlier this year, the related gold (I) phosphine complex **53,** containing a naphthalimide ligand, exhibited significant antiproliferative effects and induction of apoptosis via mitochondrial pathways, suggesting that it could be a key candidate for TrxR inhibition.[82]

Nitrosoureas



49

Phosphole complexes



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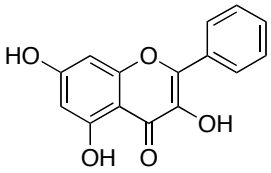
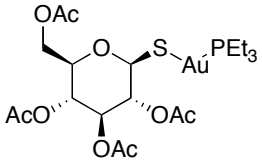
Polyphenol compounds



Curcumin flavinoids

51

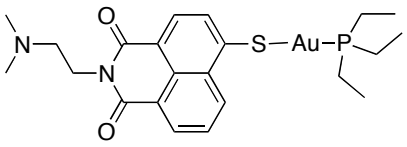
Gold (I) or (III) thiosugars



Auranofin, Au(I)

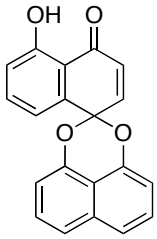
52

Naphthalimide derived gold (I) phosphine complex



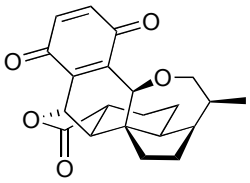
53

Quinone/ naphthoquinone compounds



Palmarumycin CP_1

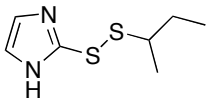
54



Pleurotin

48

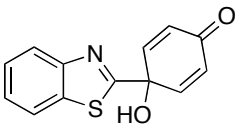
2-Imidazolyl disulfides



PX-12

55

Benzothiazole substituted quinols



AW646 (NSC 706704)

56

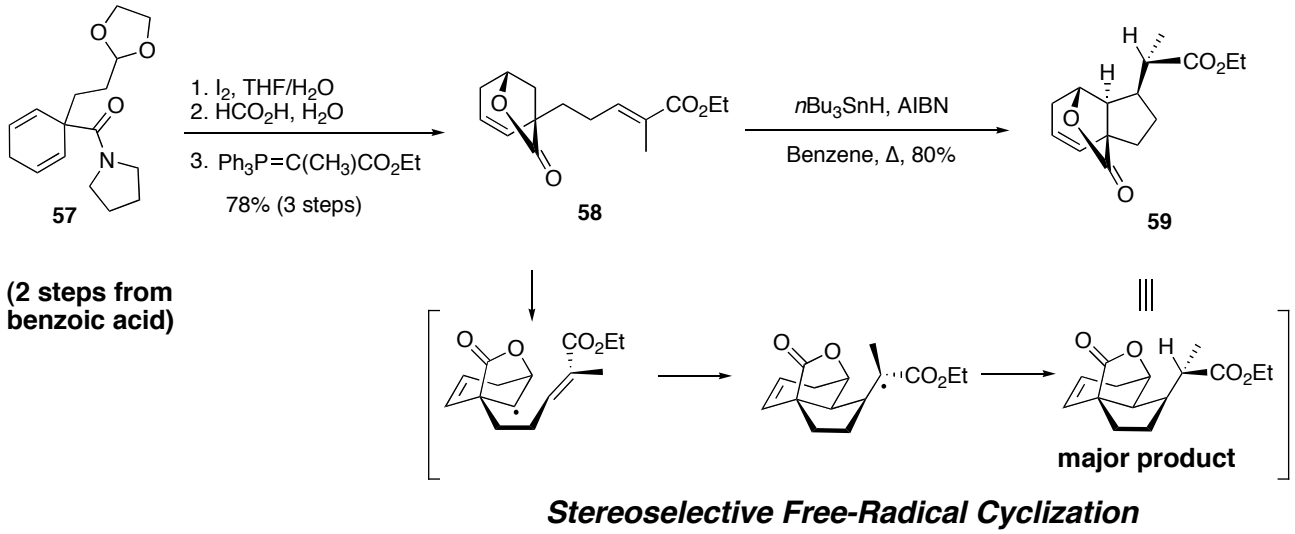
Figure 23. Known Trx/TrxR inhibitors

In 2004, Wipf and co-workers determined that palmarumycin CP_1 **(54)** is a potent inhibitor of TrxR-1/TrxR (IC_{50} = 0.35 μM), MDA-MB-231 (IC_{50} = 2.4 μM) and MCF-7 (IC_{50} = 1.0 μM) *in vitro* **(Figure 23)**.[29,75,83] Based on these findings, a library of palmarumycin CP_1 **(54)** analogs was developed demonstrating comparable inhibitory activity against Trx/TrxR to that of pleurotin **(48)** (IC_{50} = 0.17 μM).[83,84] In the late 1990's, 2-imidazoyl disulfides were identified as inhibitors of Trx/TrxR.[85] More specifically, PX-12 **(55)** was identified as an irreversible inhibitor of Trx-1. PX-12 inhibits expression of VEGF in both cells and human xenografts by preventing stimulation of transcription factor HIF-1 by Trx-1.[86] In 2004, PX-12 was the first Trx/TrxR inhibitor to enter into phase I clinical trials and studies are on going for its development as a drug candidate.[87,88] AW464 **(56)** is a novel benzothiazole substituted quinol compound that is active against colon (HCT116 and HT29), renal (CAKI-1 and ACHN), and certain breast cancer cell lines (MCF7, MDA-N, and MDA-MB435).[89]

2.1.2 Previous Synthetic Efforts of Pleurotin

2.1.2.1 Hart's racemic total synthesis

Hart and co-workers published the first total synthesis of pleurotin **(48)** in 1988.[66,90] This racemic synthesis featured a stereoselective free radical cyclization reaction that was previously developed in their research group **(Figure 24)**. Their synthesis begins with amide **57**, derived in two steps from benzoic acid, was treated with iodine in aqueous THF to form the iodo-lactone. Hydrolysis of the acetal with formic acid to generate the requisite aldehyde and conversion to the α-β-unsaturated ester under Wittig conditions gave their radical cyclization precursor **58**. Under radical conditions, **58** provided the desired tri-cycle **59** in 80% yield, the stereochemistry of which was confirmed by x-ray analysis.[66] Several functional group manipulations gave access to aldehyde **60**, which under acidic conditions gave the crude acetal **61** as a mixture of diastereomers. Subjecting this mixture to $BF_3 \cdot OEt_2$ in toluene and several additional functional group manipulations afforded the desired pentacyclic dihydropleurotin acid **(63)** in 52% yield. This late stage intermediate was then subjected to a two-step oxidation protocol to generate racemic pleurotin **(48)** in 26 total steps, and 0.3% overall yield.[66]



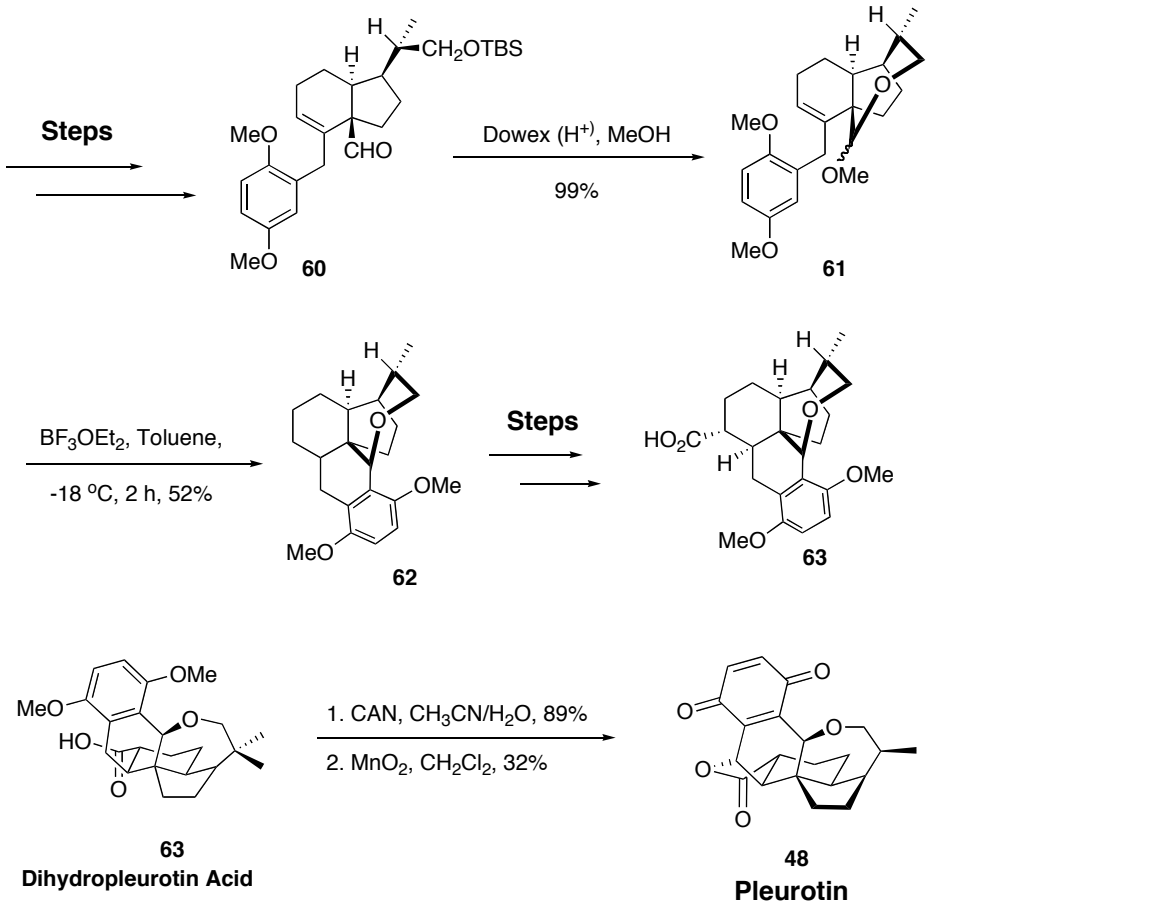


Figure 24. Hart's racemic total synthesis

2.1.2.2 Kraus' efforts toward the synthesis of pleurotin

Synthetic efforts toward the pleurotin core by the Kraus group **(Figure 25)** published in 1990 featured a tandem photo-enolization/Diels-Alder approach.[91] Aldehyde **65**, accessed in four steps from commercially available 2,5-dimethoxybenzylalcohol **(64)**, was exposed to photo-enolization conditions to initiate the radical cyclization. The subsequent thermal heating for a period of 40 h completed the tandem cyclization sequence and gave lactone **66** in 50% yield over the two steps. Silver oxide mediated oxidation generated quinone **67** in 28% yield.

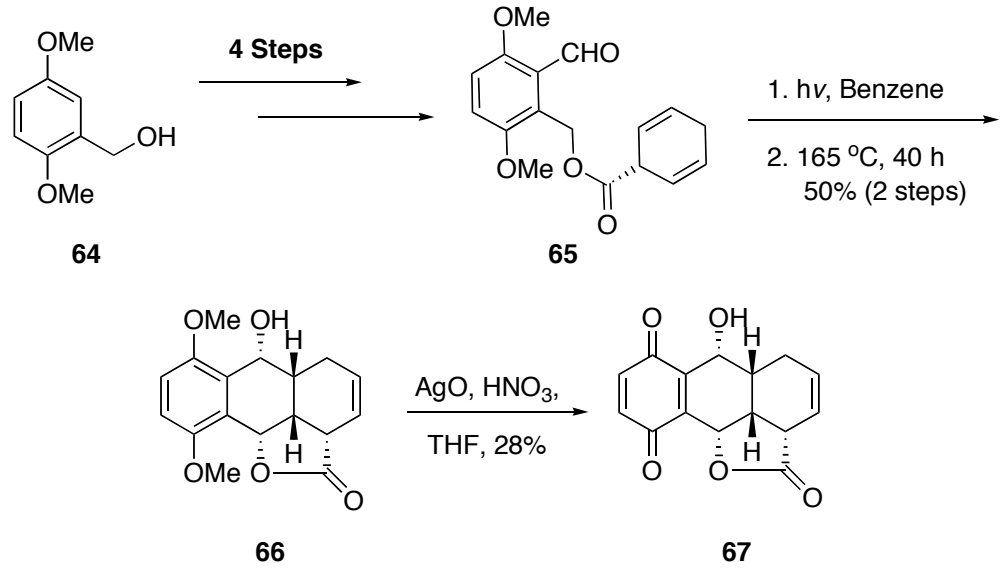
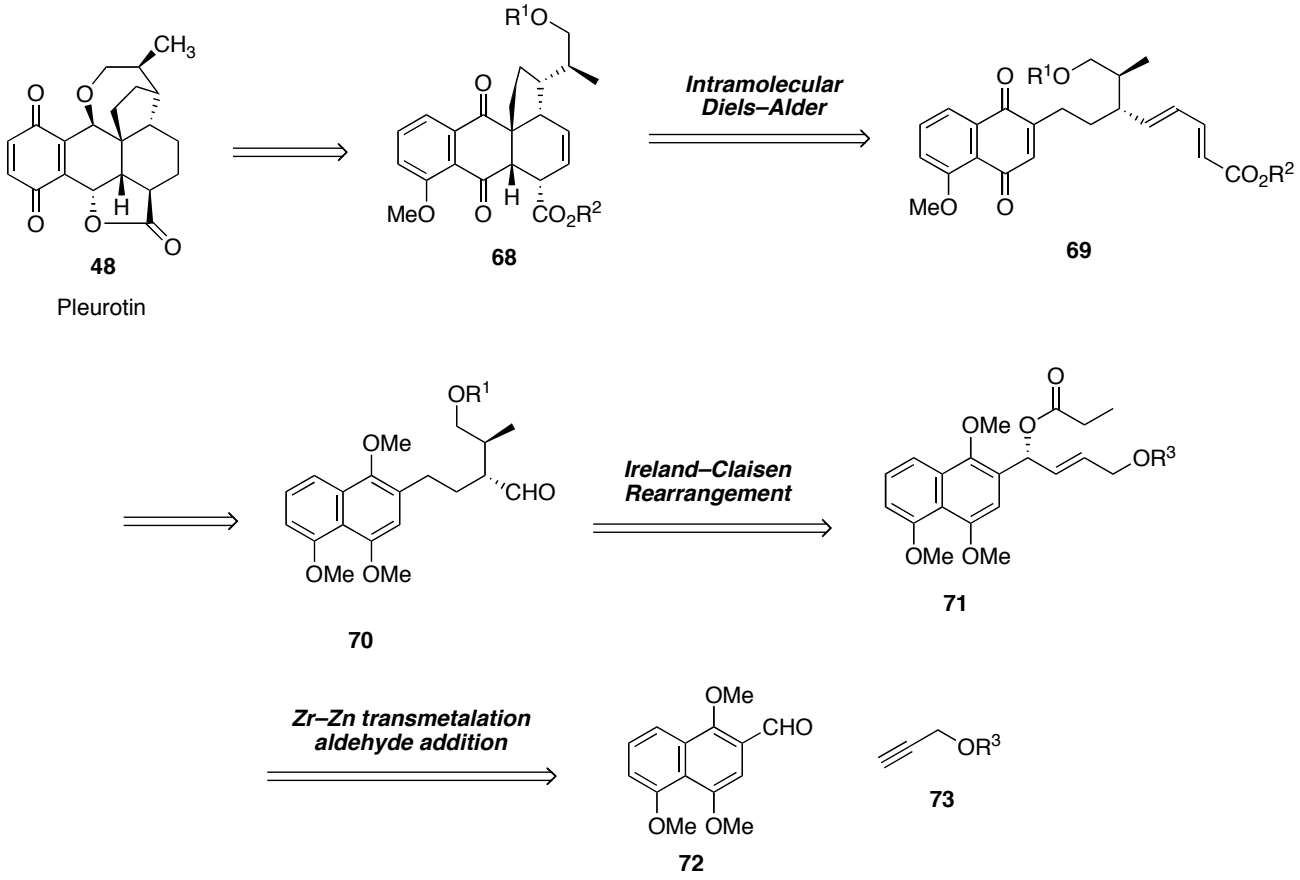


Figure 25. Kraus's approach to the pleurotin core

Although the authors did not complete the synthesis of their target molecule, the construction of four rings of the hexacyclic pleurotin core in seven chemical manipulations was quite a remarkable accomplishment. Biological evaluation of this tetracyclic quinone showed comparable activity to pleurotin **(48)** against SR Leukemia and colon cancer cell lines.[91]

2.2 SYNTHETIC EFFORTS TOWARDS PLEUORTIN BY THE WIPF GROUP

Initially, it was envisaged that **48** could be accessed via a late stage installation of the 7-membered cyclic ether, which could arise from substrate **68 (Scheme 15)**. This late stage intermediate **68** could be synthesized via an intramolecular Diels-Alder reaction arising from aldehyde **70**. This aldehyde could be generated via an Ireland Claisen rearrangement of ester **71**, which ultimately could be accessed using our Zr-Zn transmetalation addition methodology[92-96] of a suitably functionalized aldehyde **(72)** and a protected propargyl alcohol **(73)**.



Scheme 15. First generation retrosynthesis for the total synthesis of pleurotin

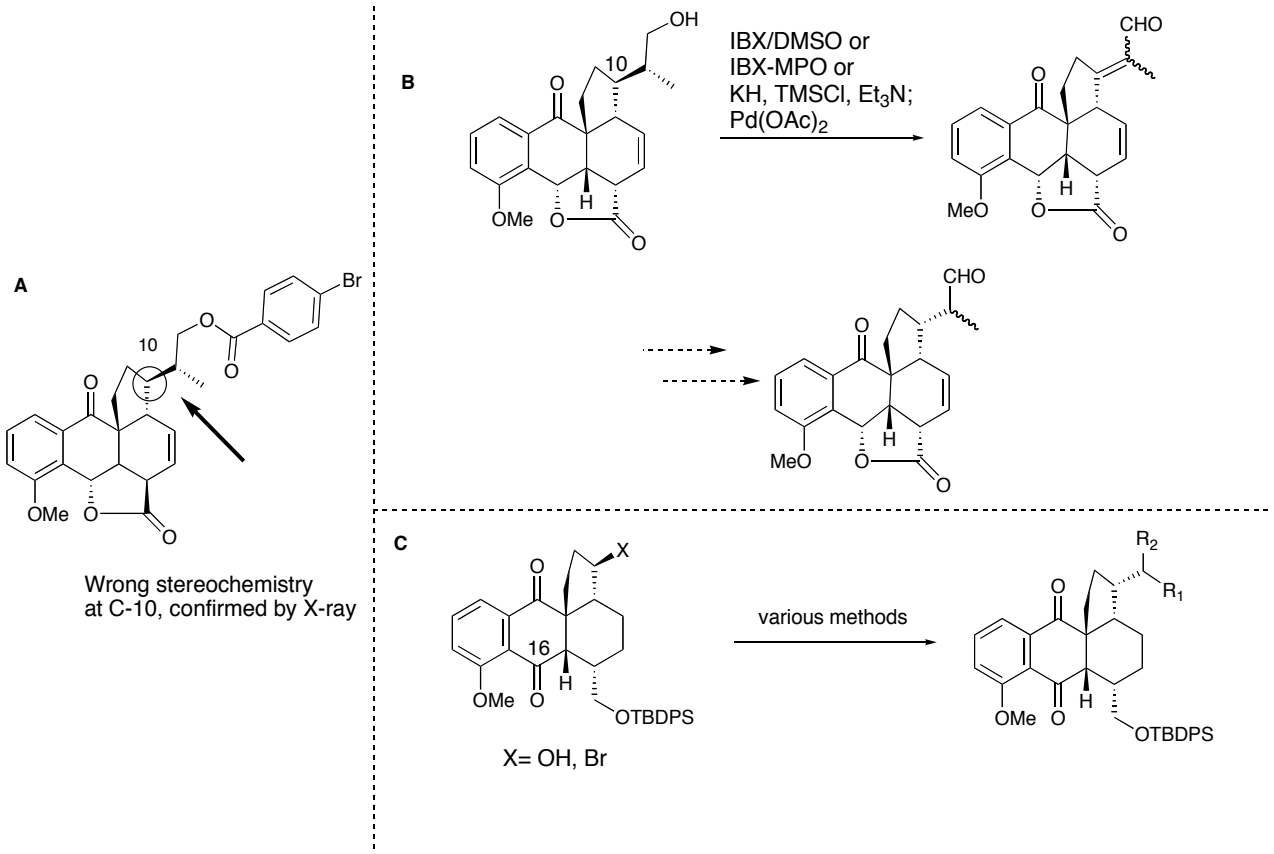


Figure 26. Attempts to the epimerize C-10 center of pleurotin

In our group's previous efforts to synthesize the fungal metabolite, pleurotin, Dr. Sonia Rodriguez,[97] Dr. Shinya Iimura,[98] and Dr. Stephan Elzner[99] faced many problems with the installation of the C_8-C_9-C_{21} side-chain and the stereochemistry at the C_{10} center. The tetracyclic core, obtained via a key intramolecular Diels-Alder reaction, afforded the incorrect stereochemistry at the C_{10} carbon **(Figure 26A)**. Subsequent attempts to epimerize this center via oxidative conditions **(Figure 26B)** or alternatively introducing the C_8-C_9-C_{21} sidechain **(Figure 26C)** proved to be unsuccessful. Evaluation of these previous attempts to correct that stereocenter led to the need to modify our approach by pursuing the pleurotin analog that does not contain the problematic stereocenter at C-9 **(Figure 27)**.

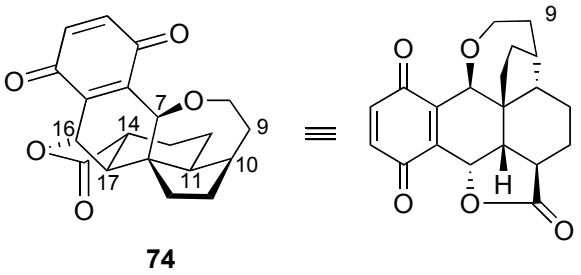
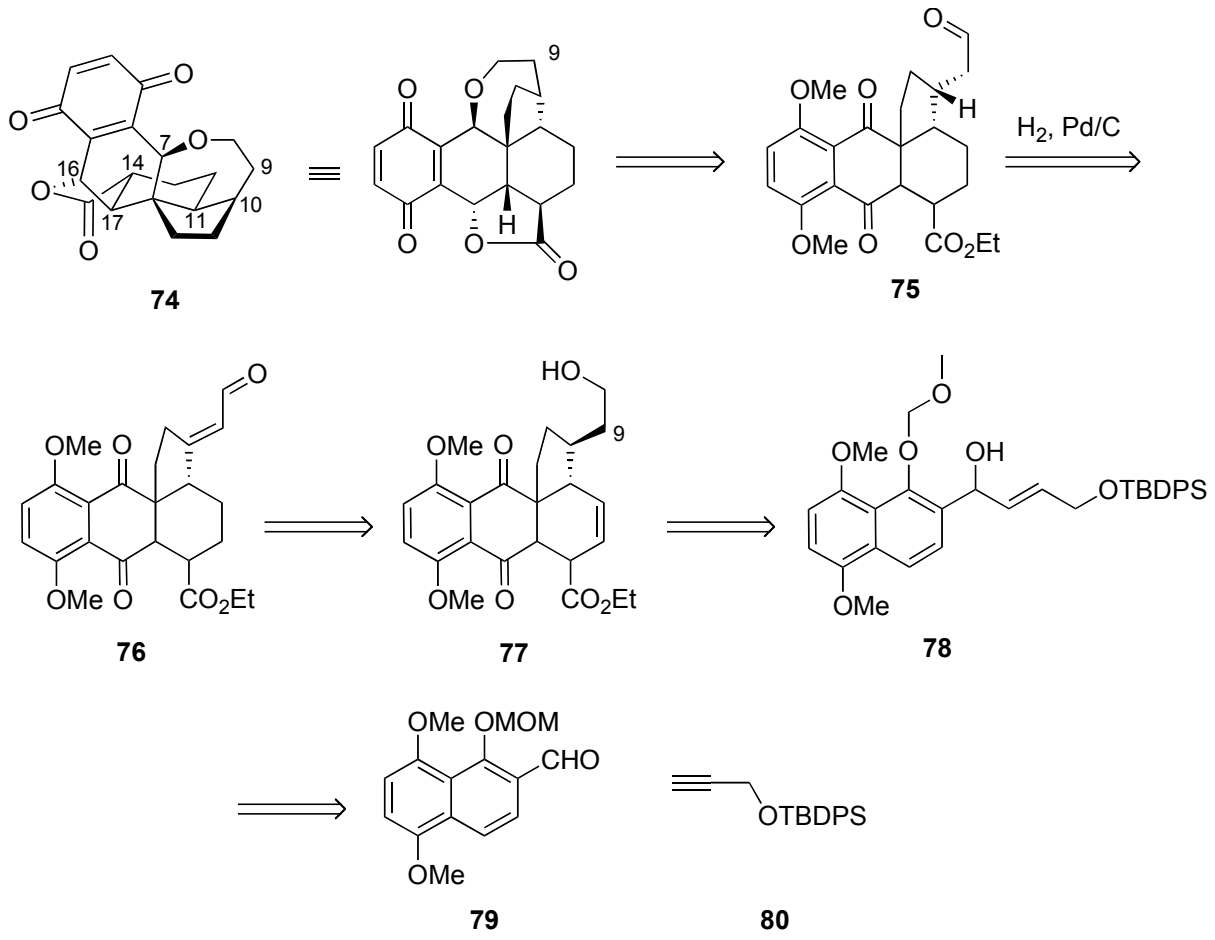


Figure 27. Structure of 9-normethylpleurotin

2.3 STUDIES TOWARD 9-NORMETHYL PLEUROTIN

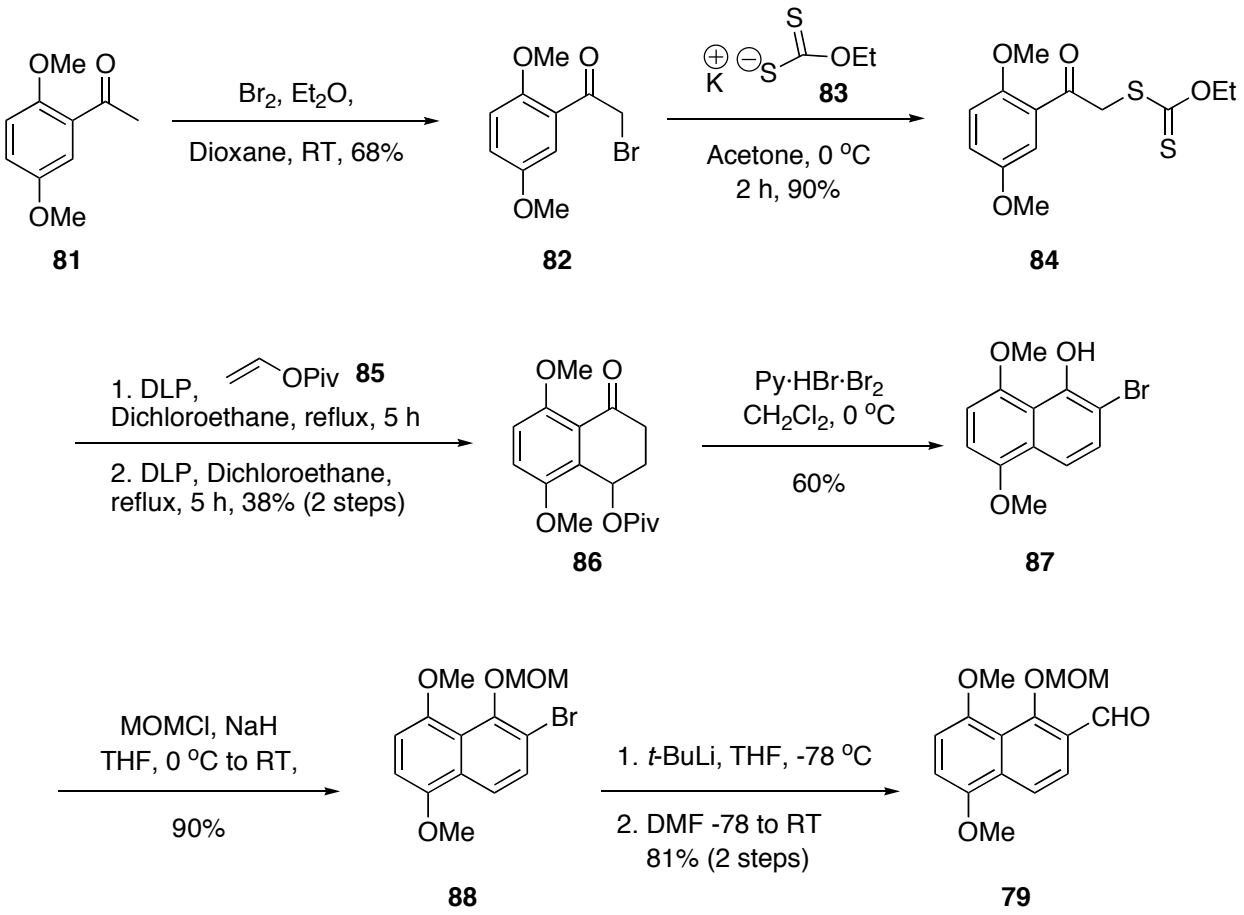
In an analogous route to what had been done previously in our labs, 9-normethylpleurotin **74** could be accessed via a late stage ring closure of the cyclic ether, which could be obtained from aldehyde **75 (Scheme 16)**. The aldehyde stereochemistry would be set through a palladium-mediated hydrogenation of naphthoquinone **76**. Synthesis of this naphthoquinone could be achieved as described previously via a Zr-Zn transmetalation/addition followed by an Ireland-Claisen rearrangement and Diels-Alder sequence.



Scheme 16. Retrosynthesis for 9-normethylpleurotin

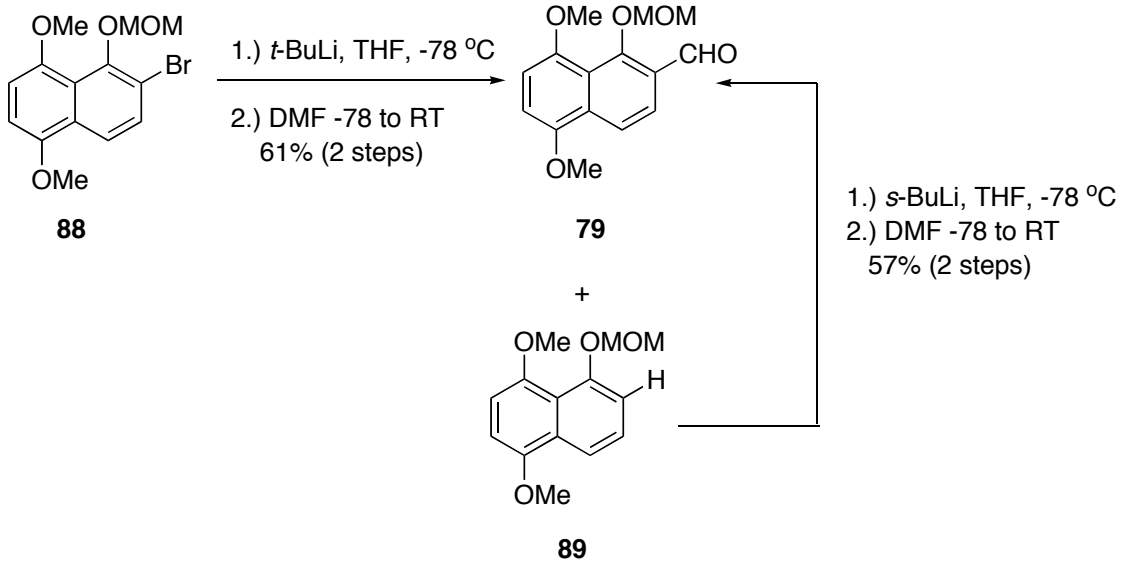
Aldehyde **79 (Scheme 17)** was synthesized starting from commercially available 2',5'-dimethoxyacetophenone **(81)**. The α-bromination of **81** was conducted via treatment with bromine in a 2:1 solution of diethylether and 1,4-dioxane in 68% yield. The resulting bromide was treated with potassium ethyl xanthate **(83)** in acetone to afford the requisite xanthate **84** in high yield. Compound **84** was then subjected to a two-step radical cyclization using Zard's protocol[100] with lauroyl peroxide (DLP) and vinyl pivalate **(85)** to give the desired tetralone **86** in 38% yield. Next aromatization of **86** to the naphthol bromide **(87)** was achieved under oxidative

pyridine perbromide conditions, and then subsequent protection of the phenol as the MOM-ether proceeded smoothly to give bromide **88**. Lastly, subjection of bromide **88** to a one-pot lithiation/formylation process afforded the desired aldehyde **(79)** in 81% yield.



Scheme 17. First generation aldehyde synthesis

In practice, the lithiation/formylation step often generated a significant quantity of the naphthol ether **89 (Scheme 18)** as a byproduct, which was attributed to the presence of water entering the system, which quenches out the lithiated species prior to formylation. We were able to sequester the formation of this side product by removing trace amounts of water from the DMF by filtration through neutral alumina immediately prior to its use. Additionally, we found that the naphthalene byproduct **89** obtained could be converted to the desired aldehyde **79** via a MOM-directed ortho-lithiation/formylation sequence.



Scheme 18. Alternate route to access aldehyde from naphthalene side product

When this first generation approach was performed on large scale (ca. 100 g of acetophenone **81**), problems arose due to the low yielding radical cyclization and the large quantity of resultant xanthate salts and peroxide by-products generated in the reaction resulting in a difficult purification. Partial removal of the xanthate salts was achieved using a repeated aqueous wash of the reaction mixture, however the greasy by-product resulting from the C_{12} carbon chain of the lauroyl peroxide reagent was very difficult to remove by chromatography

and often required multiple purifications. Attempts to purify **86** by distillation led to decomposition. In light of these technical issues with the scale up of this synthesis, an alternative approach to access aldehyde **79** was developed.

In the 1980's, H. Hart and co-workers demonstrated that tetrabromo derivatives of 1,4-disubstituted benzenes readily undergo a tandem benzyne-furan bis-annulation when treated with base in the presence of a furan to generate anthracenes **(Figure 28)**.[101-103]

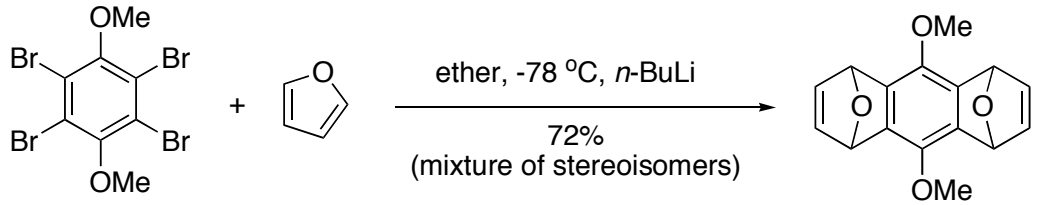


Figure 28. Anthracenes from tandem benzyne-furan bis-annulation of substituted benzenes

Martin and co-workers utilized an intramolecular tandem benzyne-furan cycloaddition to construct the anthracene core of vineomycinone B_2 **(Figure 29)**.[104] Their approach involved the construction of a benzyne precursor containing two furan silicon tethers on the substituted benzene ring. Cleavage of the tethers followed by ring opening/oxidation afforded suitably substituted anthracenes, which were then elaborated into their target natural product.

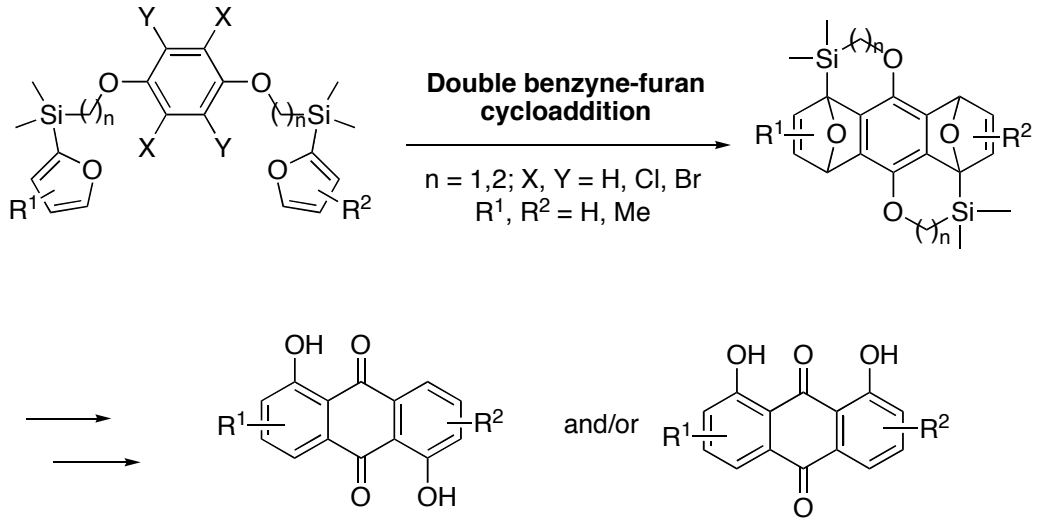


Figure 29. Martin's approach to anthracenes via a tandem benzyne-furan cycloaddition

Recently, the Kozlowski group reported the synthesis of naphthalenes involving the *in situ* generation of a benzyne intermediate that undergoes a [4 + 2]-cycloaddition with 2-methoxyfuran **(Figure 30)**.[105] The tandem ring-opening/methylation with Me_2SO_4 and K_2CO_3 in refluxing acetone afforded the highly functionalized naphthalene core of Purpuromycin 1 in good yield.

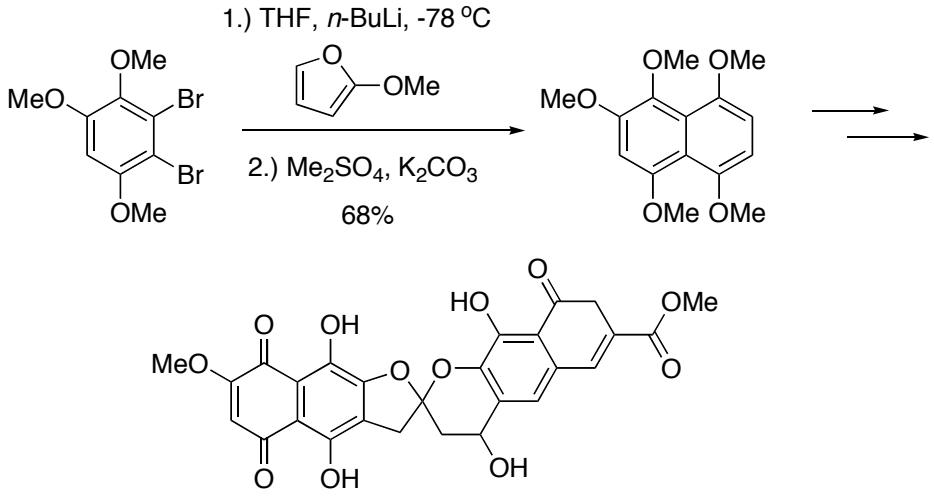
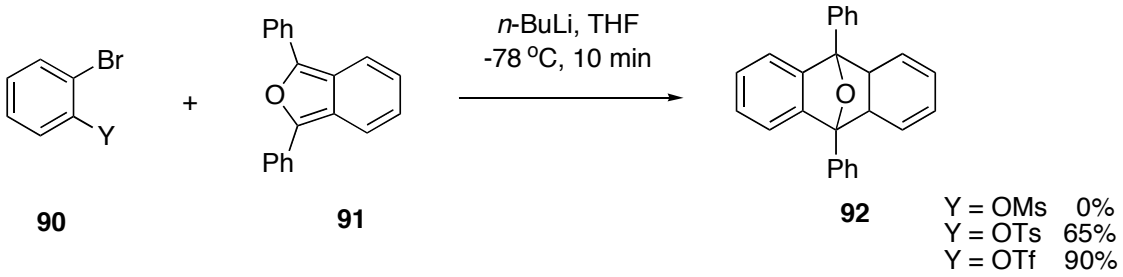


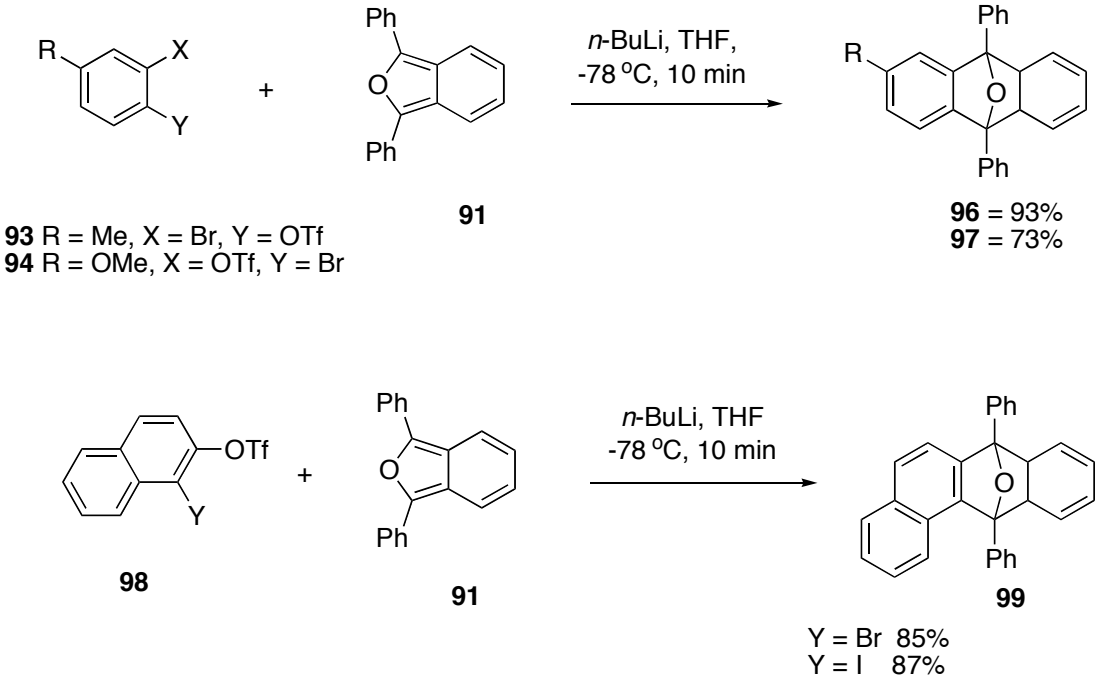
Figure 30. Accessing naphthalenes via a benzyne-furan cycloaddition

In 1991, Suzuki and co-workers were able to access naphthalenes via the *in situ* generation of a benzyne intermediate followed by [4 + 2]-cycloaddition with various substituted furans.[106] In their preliminary investigations, they explored differences in reactivity of various aryne precursors **(Scheme 19)**. Three *ortho*-bromophenyl sulfonates **90** were treated with *n*-BuLi (1.2 equiv) in THF at -78 ^{o}C in the presence of benzofuran **91** (2.0 equiv) as a trapping agent to generate compound **92**. The authors noted that both the mesylate and tosylate derivatives resulted in low yields despite the consumption of starting material. The triflate was the most promising starting material providing the desired product in 90% yield.



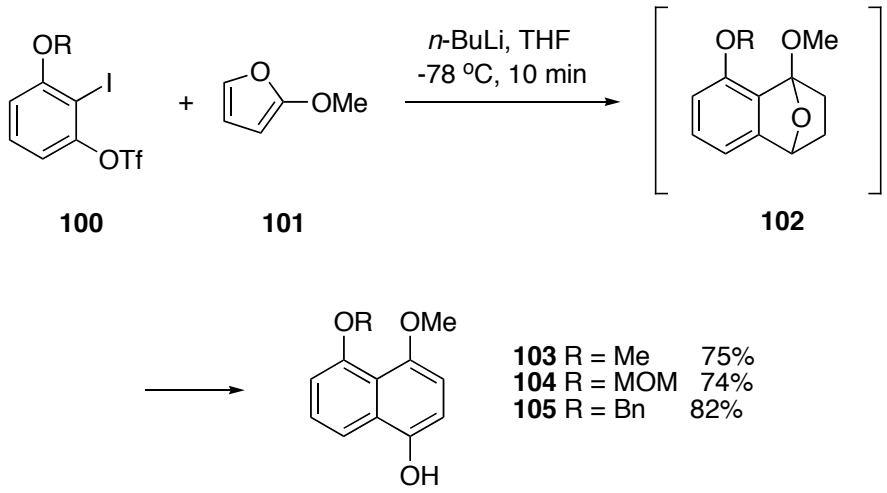
Scheme 19. Suzuki's exploration of aryne reactivity in [4 + 2] cycloaddition

Suzuki also investigated several halotriflates in this reaction manifold **(Scheme 20)**, noting that switching the positions of the halide (-Y) and the leaving group (-OTf) had essentially no effect on the yield of the reaction. Comparing the efficiency of the iodide and bromide for benzyne generation it was observed that each was an equally suitable substrate for accessing the cycloadduct **99**.



Scheme 20. Suzuki's evaluation of various halotriflates in [4 + 2] cycloaddition

In an extension of these investigations, α-alkoxyarynes were found to proceeded in an exclusive regioselective [4 + 2] cycloaddition with 2-methoxyfuran **(101)** through an analogous benzyne intermediate **(Scheme 21)**.[107] The three substrates when treated with *n*-BuLi in THF at -78 °C and an excess of 2-methoxyfuran **(101)** afforded the desired cycloaddition to give intermediate **102**, which upon aromatization provided the desired naphthols **103-105** in good yields.



Scheme 21. Accessing substituted naphthalenes via furan-benzyne [4 + 2] cycloaddition

With benzyne having been used as a reactive intermediate to quickly access highly functionalized naphthalene derivatives we wished to apply this powerful methodology to the synthesis of our key aldehyde. We imagined that a suitable halotriflate would undergo a [4 + 2]-cyclization with 2-methoxyfuran **(101)**, which upon ring opening and methylation would afford

intermediate naphthalene **106 (Figure 31)**. Compound **106** could then be subjected to directed *ortho*-lithiation/formylation conditions to afford the desired aldehyde **79**.

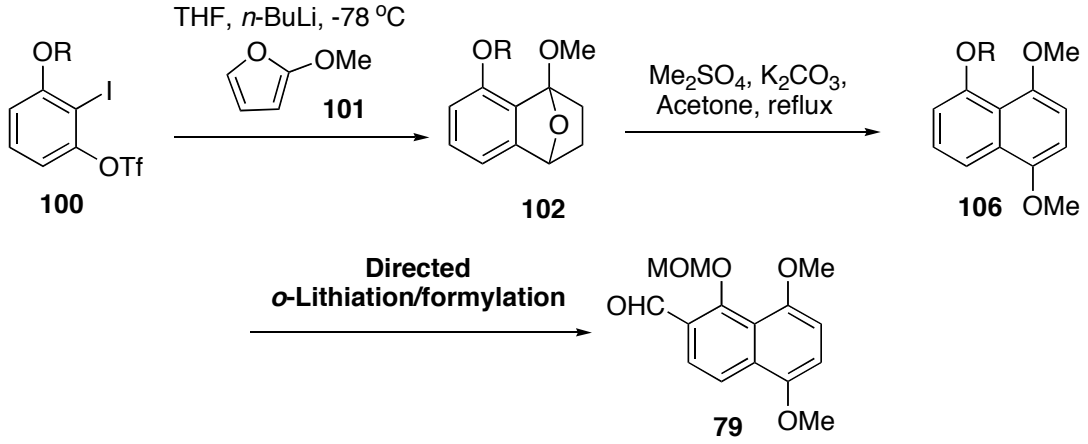


Figure 31. Utilizing a benzyne-furan cycloaddition for aldehyde synthesis

In 2007, Suzuki published an organic synthesis protocol for the preparation of benzocyclobutanone derivatives via the efficient generation of benzynes **(Figure 32)**. The protocol involved a scalable three-step synthesis of benzyne precursor **108** and showcased its utility in accessing benzocyclobutanones **110**.

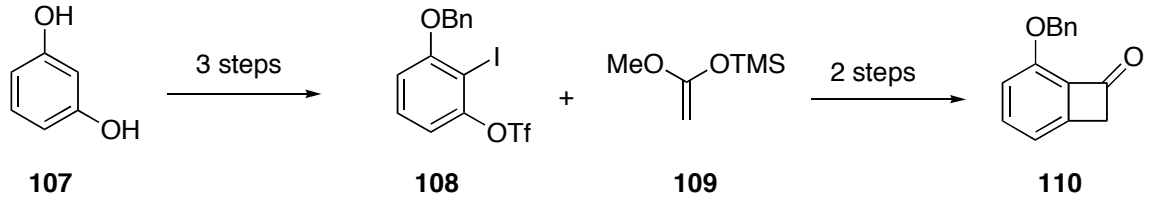
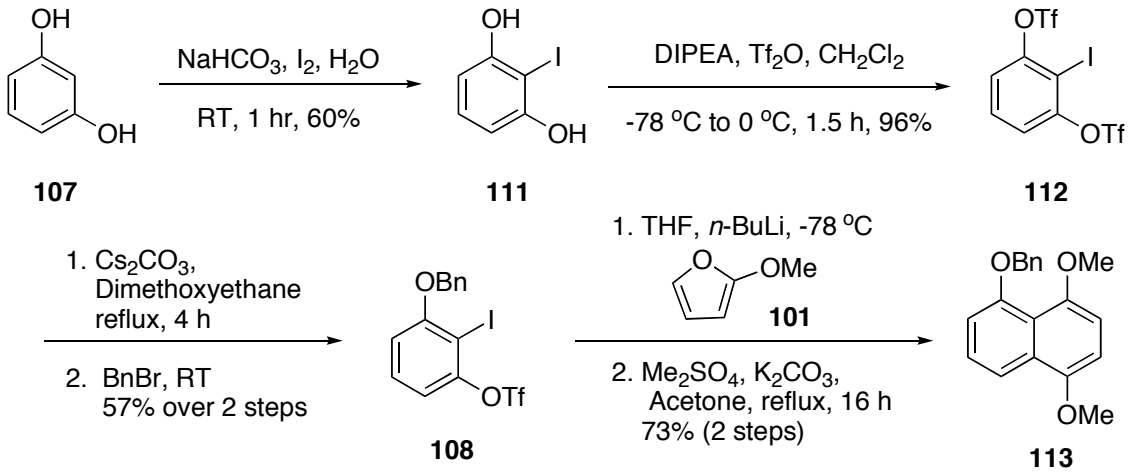


Figure 32. Suzuki's efficient synthesis of benzocyclobutanones

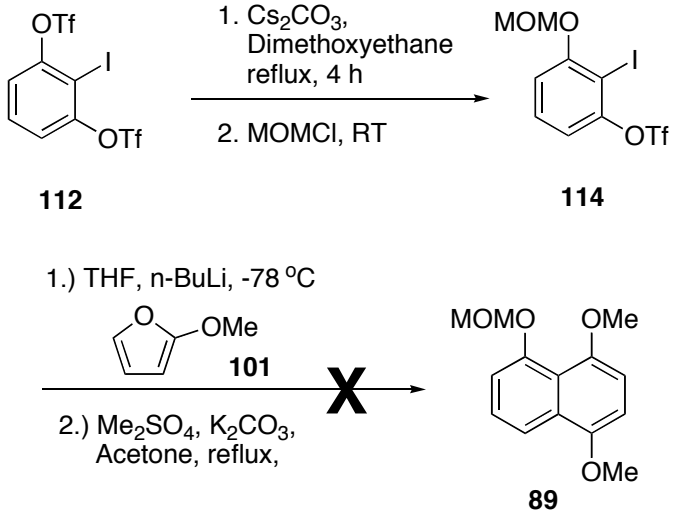
Using this three-step protocol we synthesized both the MOM- protected and benzyl-protected halotriflates to be tested in the initial cyclization sequence. The synthesis of **108** was realized in four steps from commercially available resorcinol **107 (Scheme 22)**.[107] Treatment of **107** with $NaHCO_3$ and I_2 in water generated the requisite 2-iodoresorcinol in 60% yield.

Subjecting **111** to DIPEA and Tf_2O afforded the desired compound **112** in quantitative yield. Selective mono-deprotection of the bis-triflate **112** with Cs_2CO_3 and treatment with BnBr generated compound **108** in 57% over the two steps. Pre-mixing compound **108** and 2-methoxyfuran **(101)** followed by dropwise addition of *n*-BuLi initiated the benzyne formation and immediately underwent the [4 + 2] cycloaddition. Subsequent ring opening and methylation of the free phenol afforded the desired naphthalene in 73% yield over the two steps.



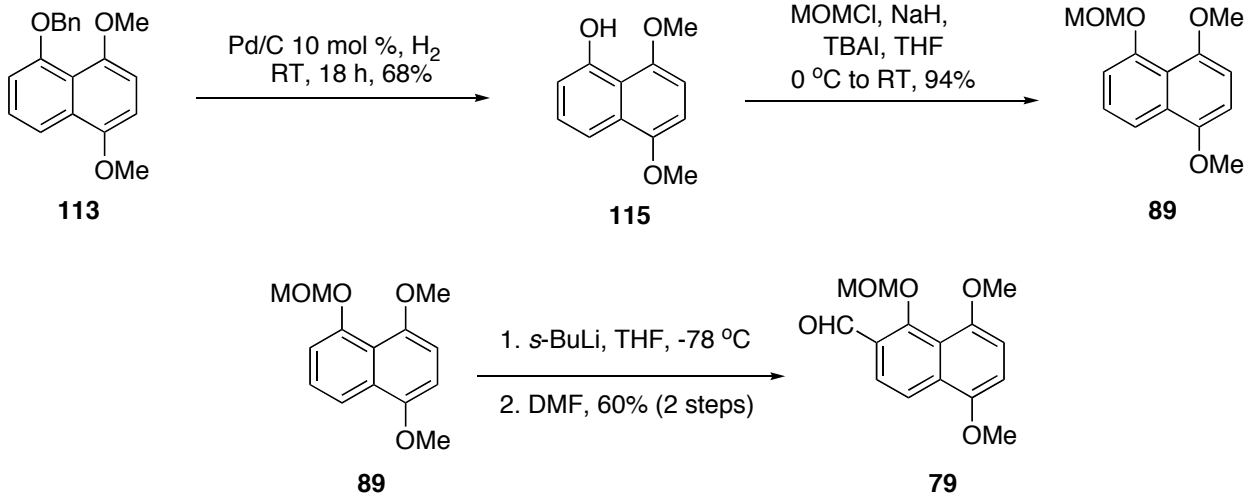
Scheme 22. Synthesis of 5-(benzyloxy)-1,4-dimethoxynaphthalene

Alternatively, 2-iodo-3-(methoxymethoxy)phenyl trifluoromethanesulfonate **114** could be synthesized via the mono-deprotection of **112** under Cs_2CO_3 conditions and subsequent protection as the MOM-ether **(Scheme 23)**. However when MOM-ether **114** was subjected to the cycloaddition/ring opening and methylation sequence the desired product **89** was not observed.



Scheme 23. Attempt to synthesize 1,4-dimethoxy-5-(methoxymethoxy)naphthalene

Thus, the synthesis of compound **89** was achieved by hydrogenolysis of benzyl-ether **113** to afford **115** and subsequent protection as the MOM-ether provided substrate **89** in good yield **(Scheme 24)**. As previously described the MOM-directed *ortho*-lithiation/formylation sequence provided aldehyde **79** in 60% yield.



Scheme 24. A second generation approach toward aldehyde 79

2.4 CONCLUSIONS

In summary, a concise second-generation synthesis of aldehyde **79** was developed utilizing a benzyne-furan [4 + 2]-cycloaddition to access the naphthalene core. Using Suzuki's organic synthesis protocol we were able to obtain the halo-triflate precursor in three steps from resorcinol. With this easily scalable substrate in hand, cycloaddition with 2-methoxyfuran proceeded nicely to generate the desired napthalene core. This alternative route to our key aldehyde not only decreased the length of the synthesis, but also eliminated the low yielding and problematic radical cyclization whose long reaction times, numerous byproducts, and difficult purifications hampered the efficient production of our key aldehyde. Studies are on going to elaborate this substrate for the synthesis of 9-normethylpleurotin **(74)**.

3.0 EXPERIMENTAL

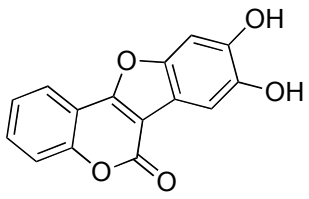
3.1 GENERAL EXPERIMENTAL

All moisture-sensitive reactions were performed under an atmosphere of nitrogen gas and all glassware was flame dried under high vacuum prior to use. Diethyl ether (Et_2O) and tetrahydrofuran (THF) were dried via distillation from Na/benzophenone. Dichloromethane (CH_2Cl_2) and toluene were purified by filtering each solvent through activated alumina columns. Reactions were monitored by thin-layer chromatography (TLC) analysis using EM Science pre-coated silica gel 60 F254 plates, 250 m layer thickness, and visualization was executed with a 254 nm UV light and by staining with a p-anisaldehyde solution (2.5 mL of p-anisaldehyde, 2.0 mL of acetic acid, and 3.5 mL of conc. sulfuric acid, in 100 mL of 95% ethanol). Flash column chromatography on SiO_2 was used to purify crude reaction mixtures. Yields refer to chromatographically and spectroscopically (^{1}H NMR) homogeneous materials unless otherwise stated.

Melting points (Mp) are uncorrected and were determined using a Laboratory Devices Mel-Temp II apparatus. Infrared spectra (IR) were obtained using a Nicolet Avatar 360 FT-IR spectrometer or a Smiths Detection IdentifyIR FT-IR spectrometer. ^{1}H and ^{13}C NMR spectra were recorded on 300 MHz/75 MHz (^{1}H/ ^{13}C NMR), 500 MHz/125 MHz (^{1}H/ ^{13}C NMR), 600 MHz/125 MHz (^{1}H/ ^{13}C NMR) using a Bruker Avance 300 MHz, a Bruker DRX 500 MHz, or a

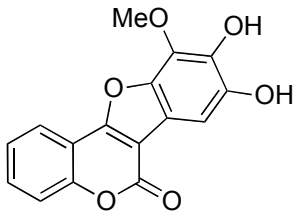
Bruker DRX 600 MHz spectrometer with 5 mM cryoprobe in $CDCl_3$ unless otherwise stated. Chemical shifts were reported in parts per million with the residual solvent peak used as an internal standard. ^1H NMR spectra, recorded at 300 MHz, 500 MHz, or 600 MHz, were tabulated as follows: chemical shift (δ), multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad), number of protons, and coupling constant(s). ^{13}C NMR spectra were recorded at 75 MHz/ 125 MHz using a proton-decoupled pulse sequence with a d_1 of 10 sec and were tabulated by observed peak. Mass spectrometry (MS) data was collected using a Micromass Autospec double focusing instrument by the University of Pittsburgh's Department of Chemistry Mass Spectrometry Facility.

3.2 LIBRARY EXPERIMENTAL



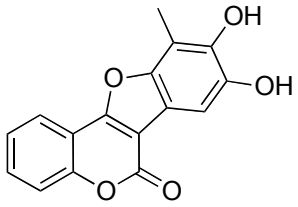
5

8,9-Dihydroxy-6H-benzofuro[3,2-c]chromen-6-one (5) (JLV1001).[32,38,46,47,108] A solution solution of NaOAc (6.0 g, 72.0 mmol), catechol (4.10 g, 36.0 mmol), and 4-hydroxycoumarin (5.92 g, 36.0 mmol) in 1:1 THF/H_2O (360 mL) was treated with $K_3Fe(CN)_6$ (35.6 g, 108.0 mmol) and stirred for 2 h. The precipitates formed were collected by vacuum filtration and recrystallized from 1:1 EtOH/Acetone to yield 3.40 g (12.7 mmol, 35%) of **5** as a tan solid powder: Mp 282 ^oC (dec.) (EtOH/Acetone); IR (neat) 3837, 3733, 3583, 3362, 3243, 2921, 2360, 2339, 2050, 1700, 1624 cm $^{-1}$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.65 (s, 1 H), 9.53 (s, 1 H), 8.01 (d, 1 H), 7.94 (d, 1 H, J = 6.9 Hz), 7.62 (t, 1 H, J = 8.1 Hz), 7.53 (t, 1 H, J = 7.2 Hz), 7.27 (s, 1 H), 7.20 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 157.9, 152.8, 149.9, 147.0, 145.2, 131.7, 125.3, 121.6, 117.5, 114.3, 112.8, 106.0, 105.3, 99.4; MS (EI) *m/z* (rel intensity) 269 $[M + 1]^+$ (17), 268 $[M]^+$ (100), 264 (14), 239 (15), 236 (21), 225 (5), 211 (6), 165 (5), 152 (6), 137 (10), 123 (14), 109 (17), 97 (30), 83 (49), 81 (30), 70 (41), 68 (53), 66 (22), 55 (72); HRMS (EI) *m/z* calcd for $C_{15}H_8O_5$ 268.0372, found 268.0371.



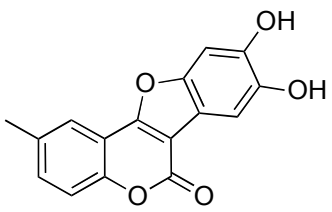
7

8,9-Dihydroxy-10-methoxy-6H-benzofuro[3,2-c]chromen-6-one (7) (JLV1009).[32] A solution of NaOAc (0.501 g, 6.0 mmol), 3-methoxycatechol (0.399 g, 3.0 mmol), 4-hydroxycoumarin (0.487 g, 3.0 mmol) in 1:1 THF/H_2O was treated with $K_3Fe(CN)_6$ (2.97 g, 9.0 mmol) and stirred for 2 h. The precipitates formed were collected by vacuum filtration and the solid was recrystallized from 1:1 EtOH/Acetone to give 0.276 g (0.925 mmol, 31%) of **7** as an orange-red powder: Mp 222.2 – 223.7 ^{o}C (Acetone); IR (neat) 3738, 3583, 3305, 3270, 2923, 1731, 1616, 1466, 1373, 1092, 1021 cm $^{-1}$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.66 (s br, 1 H), 9.14 (s br, 1 H), 8.06 (dd, 1 H, *J* = 8.0, 1.5 Hz), 7.66 (td, 1 H, *J* = 7.0, 1.5 Hz), 7.57 (d, 1 H, *J* = 8.0 Hz), 7.47 (t, 1 H, *J* = 8.0 Hz), 7.06 (s, 1 H), 4.08 (s, 1 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.0 and 157.5 (C-6 or C-11b), 152.4 (C-12), 145.9 (C-8), 141.7 (C-10a), 138.1 (C-9), 133.6 (C-10), 131.5 (C-1), 124.9 (C-4), 121.3 (C-3), 117.1 (C-2), 114.2 and 112.3 (C-4a or C-6a), 105.5 (C-11a), 99.3 (C-7), 60.6 (C-13); observed correlations in HMBC spectrum (H to C): C-1 (H-1, H-2 or H-3), C-2 (H-2, H-3), C-3 (H-2, H-3), C-4 (H-2 or H-3, H-4), C-4a (H-1, H-2), C6 (H-1, H-4), C-6a (H-2, H-3, H-7), C-7 (H-7), C-8 (H-7, H-8, H-9), C-9 (H-7, H-8, H-9), C-10 (H-7, H-9, H-13), C-10a (H-7), C-11a (H-7), C-11b (H-1, H-4), C-12 (H-1, H-2, H-3, H-4), C-13 (H-13); MS (EI) *m/z* (rel intensity) 298 $[M]^+$ (23), 287 (25), 286 (100), 283 (14), 200 (28), 194 (20), 180 (12), 165 (17), 133 (24), 117 (89), 115 (34), 105 (18), 91 (40), 89 (62), 81 (27), 69 (42), 57 (75); HRMS (EI) *m/z* calcd for $C_{16}H_{10}O_6$ 298.0477, found 298.0461.



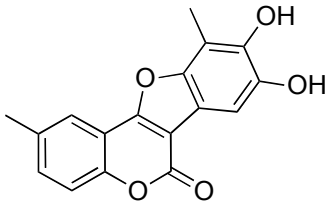
8

8,9-Dihydroxy-10-methyl-6H-benzofuro[3,2-c]chromen-6-one (8) (JLV1052).[32] A solution of NaOAc (0.332 g, 4.00 mmol), 3-methylcatechol (0.245 g, 2.00 mmol), and 4-hydroxycoumarin (0.325 g, 2.00 mmol) in 1:1 THF/H_2O (20.0 mL) was treated with $K_3Fe(CN)_6$ (1.98 g, 6.00 mmol) and stirred for 2 h. The reaction mixture was extracted with EtOAc and concentrated in vacuo. The resultant crude solid was recrystallized from 1:1 EtOH/Ether to yield 0.0976 g (0.346 mmol, 17.3%) of **8** as an orange powder: Mp 282.2 – 283.5 ^oC (dec.) (EtOH/Acetone); IR (neat) 3849, 3646, 3583, 3462, 3274, 2284, 1701 cm $^{-1}$; ^1H NMR (300 MHz, DMSO-d_6) δ 9.79 (s, 1 H), 8.94 (s, 1 H), 8.03 (d, 1 H, J = 7.5 Hz), 7.61 (m, 1 H), 7.57 (d, 1 H, J = 7.5 Hz), 7.47 (t, 1 H, J = 7.5 Hz), 7.19 (s, 1 H), 2.40 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 157.7 and 157.6 (C-6 or C-11b), 152.3 (C-12), 149.1 (C-8), 144.2 (C-9). 144.2 (C-10a), 131.2 (C-4), 124.9 (C-1), 121.2 (C-2), 117.1 (C-3), 113.0 and 112.5 (C-4a or C-6a), 108.6 (C-10), 105.7 (C-11a), 101.9 (C-7), 9.0 (C-13); correlations observed in HMBC spectrum: C-1 (H-1), C-2 (H-2), C-3 (H-3), C-4 (H-3, H-4), C-4a (H-1, H-3), C-6 (H-1, H-4), C-6a (H-1, H-3), C-7 (H-7), C-8 (H-7, H-13), C-9 (H-7, H-13), C-10 (H-13), C-10a (H-3, H-4), C-11a (H-7), C-11b (H-1, H-4), C-12 (H-1, H-2, H-4), C-13 (H-13); MS (EI) *m/z* (rel intensity) 283 $[M + 1]^+$ (31), 282 $[M]^+$ (100), 281 (15), 141 (6), 117 (7), 95 (6), 83 (8), 69 (13), 57 (17); HRMS (EI) *m/z* calcd for $C_{16}H_{10}O_5$ 282.0528, found 282.0525.



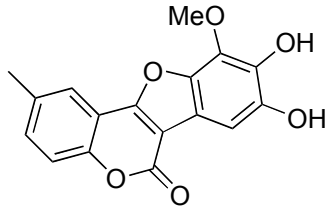
9

8,9-dihydroxy-2-methyl-6H-benzofuro[3,2-c]chromen-6-one (9) (JLV1055). A solution of NaOAc (0.329 g, 4.00 mmol), catechol (0.227 g, 2.00 mmol), and 4-Hydroxy-6-methylcoumarin (0.352 g, 2.00 mmol) in 1:1 THF/H_2O was treated with $K_3Fe(CN)_6$ (1.97 g, 6.00 mmol) and stirred for 2 hr. The reaction mixture was extracted with EtOAc and concentrated in vacuo. The resultant crude mixture was recrystallized from 1:1 EtOH/Acetone to yield 0.139 g (0.492 mmol, 25%) of **9** as a light brown solid: Mp 280 ^{o}C (dec.) (EtOH/Acetone); IR (neat) 3733, 3584, 2360, 2339, 1697, 1650, 1558, 1540, 1508, 1459, 1284 cm $^{-1}$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.63 (s, 1 H), 9.51 (s, 1 H), 7.82 (s, 1 H), 7.47 (s, 1 H), 7.28 (s, 1 H), 7.21 (s, 1 H), 2.44 (s, 1 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 158.2, 158.0, 150.9, 149.9, 146.9, 145.1, 134.8, 132.5, 121.0, 117.2, 114.3, 112.4, 105.8, 105.3, 99.3, 20.8; MS (EI) *m/z* 283 $[M + 1]^+$ (37), 282 $[M]^+$ (100), 281 (18), 253 (100), 236 (7), 141 (7), 95 (8), 83 (10), 68 (12), 55 (17); HRMS (EI) *m/z* calcd for $C_{16}H_{10}O_5$ 282.0528, found 282.0527.



10

8,9-Dihydroxy-2,10-dimethyl-6H-benzofuro[3,2-c]chromen-6-one (10) (JLV1061). A solution of NaOAc (0.987 g, 12.0 mmol), 3-methylcatechol (0.748 g, 6.00 mmol), and 4-Hydroxy-6-methylcoumarin (1.10 g, 6.00 mmol) in 1:1 THF/H_2O (60.0 mL) was treated with $K_3Fe(CN)_6$ (5.93 g, 18.00 mmol) and stirred for 2 hr. The reaction mixture was extracted with EtOAc, dried ($MgSO_4$), and concentrated in vacuo. The resultant crude mixture was recrystallized from 1:1 EtOH/Acetone to yield 0.547 g (1.85 mmol, 31%) of **10** as a brown solid: Mp 275 ^{o}C (dec.) (EtOH/Acetone); IR (neat) 3740, 3582, 3398, 2919, 1644, 1023 cm $^{-1}$; ^{1}H NMR (500 MHz, DMSO-d_6) δ 9.78 (s, 1 H), 8.92 (s, 1 H), 7.77 (s, 1 H), 7.42 (s, 2 H), 7.16 (s, 1 H), 2.42 (s, 3 H), 2.38 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.2 and 158.1 (C-6 or 11b), 151.0 (C-12), 149.5 (C-10a), 144.6 and 144.6 (C-8 andC-9), 134.8 (C-2), 132.6 (C-1), 121.1 (C-3), 117.3 (C-4), 113.5 and 112.6 (C-4a and C-6a), 109.0 (C-10), 106.1 (C-11a), 102.3 (C-7), 20.8 (C-14), 9.5 (C-13); Observed HMBC correlations: C-1 (H-14), C-2 (H-3, H-4, H-14), C-3 (H-3, H-4, H-14), C-7 (H-8), C-8 (H-7, H-8, H-13), C-9 (H-7, H-9, H-13), C-11a (H-7), C-12 (H-1, H-3, H-4), C-13 (H-13), C-14 (H-14); MS (EI) *m/z* (rel intensity) 298 $[M + 2]^+$ (6), 297 $[M + 1]^+$ (54), 296 $[M]^+$ (100), 295 (26), 267 (9), 165 (14), 148 (20), 141 (29), 134 (13), 128 (10), 115 (13), 105 (7), 77 (15), 63 (11); HRMS (EI) *m/z* calcd for $C_{17}H_{12}O_5$ 296.0685, found 296.0678.

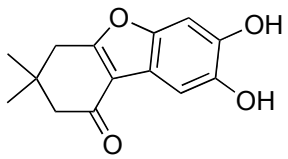


11

8,9-Dihydroxy-10-methoxy-2-methyl-6H-benzofuro[3,2-c]chromen-6-one (11)

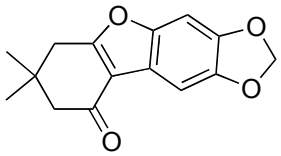
(JLV1066).[39] A solution of NaOAc (0.328 g, 4.00 mmol), 3-methoxycatechol (0.300 g, 2.00 mmol), 4-Hydroxy-6-methylcoumarin (0.353 g, 2.00 mmol) in 1:1 THF/H_2O (20.0 mL) was treated with $K_3Fe(CN)_6$ (1.98 g, 6.00 mmol) and stirred for 2 hr. The reaction mixture was extracted with EtOAc, dried ($MgSO_4$), and concentrated. The resultant crude mixture was triturated with 1:1 EtOH/Ether to yield 0.090 g (0.288 mmol, 15%) of **11** as an orange solid: Mp 198 ^oC (dec.) (EtOH/Ether); IR (neat) 3583, 3367, 2917, 2849, 2360, 2339, 1650, 1576, 1540, 1420, 1362, 1068 cm $^{-1}$; ^1H NMR (500 MHz, DMSO-d_6) δ 9.64 (s, 1 H), 9.12 (s, 1 H), 7.85 (s, 1 H), 7.45 (s, 2 H), 7.04 (s, 1 H), 4.07 (s, 3 H), 2.49 (s, 3 H); ^{13}C NMR (125 MHz, DMSO-d_6) δ 158.5 and 158.1 (C-6 or C-11b), 151.1 (C-12), 146.3 (C-8), 142.2 (C-10a), 138.6 (C-9), 135.0 (C-2), 134.1 (C-10), 132.9 (C-1), 121.3 (C-4), 117.3 (C-3), 114.8, 112.5 (C-4a or C-6a), 105.9 (C-11a), 99.8 (C-7), 61.1 (C-13), 20.8 (C-14); observed correlations in HMBC spectrum (H to C): C-1 (H-1), C-2 (H-3, H-4), C-3 and C-4 (H-3 or H-4), C-4a (H-3, H-4), C-6 (H-3, H-4), C-6a (H-1, H-3, H-4), C-7 (H-8), C-8 (H-7, H-8, H-9), C-9 (H-7, H-8, H-9), C-10 (H-7, H-9, H-13), C-10a (H-7), C-11a (H-7), C-11b (H-1, H-3, H-4), C-12 (H-1, H-3, H-4, H-14), C-13 (H-13), C-14 (H-14); MS (EI) *m/z* (rel intensity) 313 $[M + 1]^+$ (14), 312 $[M]^+$ (52), 297 (30), 296 (12), 269 (10), 264 (13), 239 (15), 213 (8), 200 (5), 185 (8), 176 (28), 171 (12), 161 (20), 160 (45), 148 (21), 141 (13), 135 (20), 134 (46), 129 (25), 123 (16), 117 (40), 109 (24), 105 (20), 97 (40), 91

(27), 85 (33), 83 (54), 81 (49), 77 (30), 71 (53), 69 (82), 67(40), 60 (21), 57 (100); HRMS (EI) *m/z* calcd for $C_{17}H_{12}O_6$ 312.0632, found 312.0634.



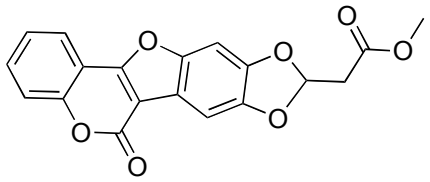
13

7,8-dihydroxy-3,3-dimethyl-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-one (13) (JLV1081).[46,108] A 1 L round bottom flask was charged with catechol (4.98 g, 45.3 mmol), 5,5-dimethylcyclohexane-1,3-dione (9.52 g, 68.0 mmol), and $NaHCO_3$ (4.20 g, 50.0 mmol) and dissolved in H_2O (200 mL). To the stirred solution was added a solution of $K_3Fe(CN)_6$ (24.7 g, 75.0 mmol) in H_2O (200 mL) via an addition funnel. As the iron solution was added dropwise a blue color appeared and then disappeared with each drop and immediately precipitates began to form, turning the clear solution to a milky white. The reaction mixture was stirred for 3 hrs and the suspension was then vacuum filtered. The resultant solid was washed with water and recrystallized from 1:1 EtOH/Acetone to yield 4.68 g (19.0 mmol, 42%) of **13** as a white solid: Mp 180 ^{o}C (dec.) (EtOAc); IR (neat) 3848, 3814, 3583, 3305, 2922, 2852, 2359, 2048, 1646, 1457, 1075 cm $^{-1}$; ^{1}H NMR (300 MHz, DMSO-d_6) δ 9.12 (s, 2 H), 7.19 (s, 1 H), 6.97 (s, 1 H), 2.87 (s, 2 H), 2.37 (s, 2 H), 1.08 (s, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 193.7, 168.7, 148.4, 144.4, 143.8, 114.5, 114.3, 105.4, 98.5, 51.6, 36.8, 35.0, 28.1; MS (ES) *m/z* (rel intensity) 247 $[M + 1]^+$ (14), 246 $[M]^+$ (77), 237 (28), 208 (44), 199 (24), 190 (100), 162 (100), 134 (13), 115 (16), 97 (25), 91 (29), 78 (39), 69 (70), 67 (35), 63 (23), 57 (91), 55 (100); HRMS (EI) *m/z* calcd for $C_{14}H_{14}O_4$ 246.0892, found 246.0885.



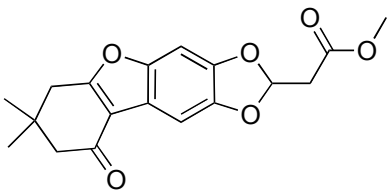
14

Formylidene protected 7,8-Dihydroxy-3,3-dimethyl-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-one (14) (JLV1086). A solution of compound **13** (2.46 g, 10.0 mmol) and cesium carbonate (2.90 g, 15.0 mmol) in anhydrous DMF (24.0 mL) was treated with $BrCH_2Cl$ (1.0 mL, 15.0 mmol) and refluxed for 4.5 h. Once cool, reaction mixture was poured over water and extracted with ether. The organic extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The resultant solid was purified by flash chromatography on SiO_2 (R_f = 0.40, $CHCl_3$, 100 %) to yield 0.600 g (2.32 mmol, 23%) of **14** as a white solid: Mp 250 ^oC (dec.) ($CHCl_3$); IR (neat) 3818, 3742, 3672, 3583, 3366, 2920, 2361, 1663, 1457, 1135, 1040, 859 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1 H), 6.93 (s, 1 H), 5.98 (s, 2 H), 2.82 (s, 2 H), 2.31 (s, 2 H), 1.59 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.2, 169.0, 150.0, 146.3, 145.5, 117.0, 115.7, 101.5, 100.5, 93.6, 52.2, 37.8, 35.3, 28.7; MS (EI) *m/z* (rel intensity) 259 $[M + 1]^+$ (18), 258 $[M]^+$ (94), 203 (19), 202 (74), 175 (17), 174 (100), 146 (13), 88 (10), 77 (9), 69 (13), 63 (9); HRMS (EI) *m/z* calcd for $C_{14}H_{14}O_4$ 258.0892, found 258.0893.



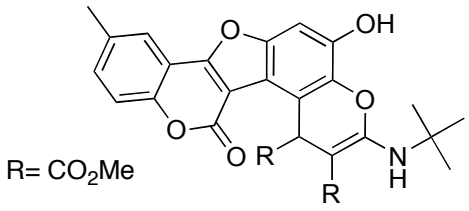
16

Moc-ethylidene acetal of 8,9-Dihydroxy-6H-benzofuro[3,2-c]chromen-6-one (16) (JLV1113).[48] A solution of compound **5** (0.300 g, 1.10 mmol) in CH_3CN (10.0 mL) was treated with methyl propiolate (91 μL, 1.10 mmol) and DMAP (0.186 g, 1.5 mmol) and stirred at rt for 2 h. The reaction mixture was concentrated in vacuo and the resultant crude residue was purified by flash chromatography on SiO_2 (R_f = 0.50, Hex/EtOAc, 3:1) to yield 0.0750 g (0.204 mmol, 21%) of **16** as a white solid: Mp 194.2 - 197.4 ^oC (Hexane/EtOAc); IR (neat) 2922, 2360, 2339, 1738, 1626, 1508, 1469, 1360, 1272, 1148, 1070, 1030, 756 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, 1 H, *J* = 7.8 Hz), 7.53 (t, 1 H, *J* = 7.2 Hz), 7.45 (d, 1 H, *J* =7.5 Hz), 7.36 (t, 1 H, *J* =7.8 Hz), 7.24 (s, 1 H), 7.10 (s, 1 H), 6.63 (t, 1 H, *J* = 5.1 Hz), 3.77 (s, 3 H), 3.05 (d, 2 H, *J* = 5.1 Hz); ^{13}C NMR (75 MHz, $CDCl_3$) δ 168.5, 159.2, 158.1, 153.0, 151.0, 147.4, 145.9, 131.2, 124.6, 121.3, 117.4, 117.0, 112.8, 109.2, 106.4, 94.1, 52.3, 40.0; MS (EI) *m/z* (rel intensity) 353 $[M + 1]^+$ (20), 352 $[M]^+$ (92), 320 (23), 303 (8), 292 (14), 279 (97), 268 (25), 267 (20), 265 (10), 239 (10), 200 (16), 137 (13), 109 (13), 97 (25), 84 (84), 81 (47), 69 (100), 57 (66); HRMS (EI) *m/z* calcd for $C_{19}H_{12}O_7$ 353.0661, found 353.0689.



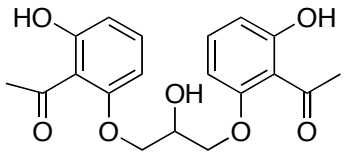
17

Moc-ethylidene acetal of 7,8-Dihydroxy-3,3-dimethyl-3,4-dihydrodibenzo[*b*,*d*]furan-1(2*H*)-one (16) (JLV1103).[48] A solution of compound **13** (0.481 g, 1.90 mmol) in CH_3CN (15.0 mL) was treated with methyl propiolate (200 μL, 2.41 mmol) and DMAP (0.3823 g, 2.28 mmol) and stirred at room temperature for 1 h. The reaction mixture was concentrated in vacuo and the resultant crude residue was purified by flash chromatography on SiO_2 (R_f = 0.40, Hex/EtOAc, 3:1) to yield 0.269 g (0.814 mmol, 43%) of **17** as white solid: Mp 149.1 - 151.3 ^oC (Hexane/EtOAc); IR (neat) 2955, 1743, 1670, 1497, 1464, 1437, 1403, 1305, 1272, 1134, 1087, 1039 cm $^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 7.39 (s, 1 H), 6.92 (s, 1 H), 6.62 (t, 1 H, *J* = 5.4 Hz), 3.75 (s, 3 H), 3.06 (d, 2 H, *J* = 5.4 Hz), 2.83 (s, 2 H), 2.42 (s, 2 H), 1.16 (s, 6 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 194.3, 169.2, 168.8 150.1, 145.9, 145.3, 117.2, 115.9, 108.7, 100.8, 93.8, 52.4, 52.3, 40.1, 38.0, 35.5, 28.9, 28.8; MS (EI) *m/z* (rel intensity) 331 $[M + 1]^+$ (12), 330 $[M]^+$ (65), 279 (9), 274 (15), 258 (11), 257 (65), 246 (22), 231 (6), 213 (13), 185 (14), 157 (15), 149 (43), 137 (85), 136 (53), 129 (33), 123 (48), 121 (53), 109 (48), 107 (36), 105 (24), 97(42), 95 (100); 93 (64), 91 (52); HRMS (EI) *m/z* calcd for $C_{18}H_{18}O_6$ 330.1103, found 330.1097.



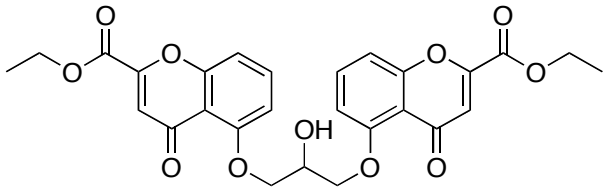
20

JLV1123 (20).[49,50] 8,9-dihydroxy-2-methyl-6H-benzofuro[3,2-c]chromen-6-one **(9)** (0.571 g, 2.0 mmol) was added to CH_2Cl_2 (10.0 mL) and THF (0.5 mL). The flask was cooled to -5 ^oC and DMAD (250 μL, 2.0 mmol) was added via syringe. The reaction mixture was stirred for 5 min and then t-Butyl isocyanide (191 μL, 2.0 mmol) was added dropwise slowly and stirred for 10 min at -5 ^oC before warming to rt. The reaction was stirred at rt for 48 h and concentrated. The crude mixture was purified by flash chromatography on SiO_2 (R_f = 0.20, Hex/EtOAc, 4:1) to yield 0.301 g (0.594 mmol, 30%) of **20** as a white solid: Mp 153.0 – 156.0 ^oC (CH_2Cl_2); IR (neat) 3582, 3367, 2923, 1740, 1664, 1616, 1476, 1435, 1380, 1318, 1258, 1209, 1134, 1073, 1031 cm^{-1}; ^1H NMR (500 MHz, $CDCl_3$) δ 9.10 (br s, 1 H), 7.83 (s, 1 H), 7.79 (s, 1 H), 7.40 (s, 1 H), 7.34 (s, 1 H), 5.92 (s, 1 H), 3.77 (s, 3 H), 3.75 (s, 3 H), 2.49 (s, 3 H) 1.59 (s, 9 H), 1.53 (s, 9 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 170.7, 169.6 (C-20 and C-21), 169.3 (C-10), 160.9 (C-6), 158.3 (C-17b), 153.2 (C-16), 151.9 (C-4a), 147.0 (C-6a), 141.3 (C-14), 134.9 (C-2), 133.2 (C-18), 121.6 (C-4), 117.4 (C-3), 114.0 (C-13), 112.4 (C-1), 105.9 (C-8), 103.7 (C-15), 82.4 (C-11), 73.5 (C-9), 53.5, 52.9 (C-22 and C-23), 51.6 (C-25), 31.2 (C-24), 21.2 (C-19); Relevant HMBC correlations: C-6a [H-1, H-9, H-15]; MS (EI) *m/z* 507 (M^+,10), 448 (100), 392 (96), 360 (45), 349 (30), 281 (55), 261 (5), 138 (6), 91 (10), HRMS (EI) *m/z* calcd for $C_{27}H_{25}NO_9$ 507.1529, found 507.1537.



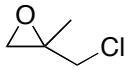
30

1,1'-(6,6'-(2-Hydroxypropane-1,3-diyl)bis(oxy)bis(2-hydroxy-6,1-phenylene))diethanone (30). A solution of 2,6-dihydroxyacetophenone **(28)** (9.70 g, 64.0 mmol) and epichlorohydrin **(29)** (2.67 mL, 33.8 mmol) was dissolved in hot i-PrOH (250 mL) and heated to 80 ^{o}C. To the reaction mixture was added a solution of KOH (2.3 g, 40.2 mmol) in i-PrOH (25.0 mL) and H_2O (1.0 mL). After refluxing for 46 h, H_2O (50.0 mL) was added to the cooled reaction mixture. The resultant precipitate was filtered off and washed with ether and water and the resultant solid was recrystallized from hot i-PrOH and dried under vacuum overnight to give product 4.4 g (12.2 mmol, 36%) of **30** as a light tan solid: Mp 163.0 – 170.0 ^{o}C (CH_2Cl_2); IR (ATR) (neat) 3517, 3511, 3490, 2944, 2939, 2915, 2626, 1618, 1593, 1446, 1364, 1346, 1251, 1234, 1176, 1105, 1083, 1070, 1020, 956 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 7.32 (t, 2 H, *J* = 8.1 Hz), 6.57 (d, 2 H, *J* = 8.4 Hz), 6.50 (d, 2 H, *J* = 8.1 Hz), 5.49 (d, 1 H, *J* = 4.8 Hz), 4.25 (m, 1 H), 4.12 (m, 4 H), 2.57 (s, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.0, 160.4, 159.0, 134.5 113.8, 109.6, 103.0, 70.3, 67.1, 33.3; MS (EI) *m/z* (rel intensity) 360 $[M]^+$ (25), 342 (26), 209 (8), 196 (40), 165 (87), 137 (100), 107 (24), 69 (23); HRMS (EI) *m/z* calcd for $C_{19}H_{20}O_7$ 360.1209, found 360.1213.



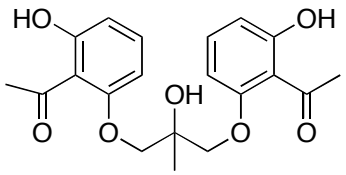
32

Diethyl-5,5'-(2-hydroxypropane-1,3-diyl)bis(oxy)bis(4-oxo-4H-chromene-2-carboxylate) (32).[54,55] Sodium metal (0.459 g, 19.9 mmol) was dissolved in EtOH (10.0 mL) and heated to reflux. To the hot solution was added solid bis-phenol **30** (0.720 g, 1.99 mmol) and diethyl oxalate **(31)** (1.66 mL, 11.9 mmol) and refluxed for 20 h. Once cooled, the reaction mixture was poured into ether and filtered. The resultant solid was added to water (12.0 mL) and acidified with 1.0 M HCl. The aqueous mixture was extracted with CH_2Cl_2 and the organic extracts were combined, dried ($MgSO_4$) and concentrated in vacuo. To the resultant residue was added conc. HCl (0.500 mL) and heated in an oil bath for 5 min. The reaction mixture was filtered and solids were recrystallized with 1:1 EtOH/Benzene (6.0 mL). The resultant brown solid product was dried under vacuum overnight to give 0.490 g (0.935 mmol, 47%) of **32** as a brown solid: Mp 180.0 – 185.1 ^{o}C (EtOH); IR (ATR) (neat) 3459, 3466, 3097, 3082, 2611, 2380, 2397, 1733, 1640, 1616, 1599, 1569, 1560, 1474, 1457, 1450, 1388, 1264, 1241, 1215, 1124, 1073, 1049, 1012, 950, 868 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 7.71 (t, 2H, *J*= 8.4 Hz), 7.13 (dd, 4H, *J*= 19.8, 8.4 Hz), 6.67 (s, 2H), 4.28 (m, 8H), 1.32 (t, 6H, *J*= 5.7 Hz); MS (EI) *m/z* (rel intensity) 524 $[M]^+$ (15), 496 (14), 368 (7), 234 (9), 206 (13), 121 (22), 97 (27), 83 (40), 69 (75), 57 (100); HRMS (EI) *m/z* calcd for $C_{27}H_{24}O_{11}$ 524.1319, found 524.1329.



34

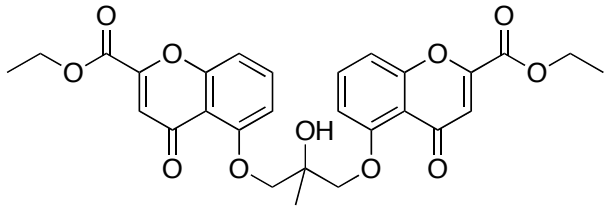
2-(Chloromethyl)-2-methyloxirane (34).[56] A solution of 3-chloro-2-methylpropene **(33)** (5.4 mL, 49.7 mmol) in dry CH_2Cl_2 (100 mL) was treated with *m*-CPBA (8.57 g, 50.0 mmol) and stirred at RT overnight. The reaction mixture was washed with saturated sodium bicarbonate solution (4 x 25.0 mL) and brine and dried ($MgSO_4$). The clear colorless liquid was carefully concentrated in vacuo until about 6.0 mL of liquid remaining and distilled (50 ^oC) to give 5.10 g (47.8 mmol, 96%) of **34** as a clear colorless liquid: ^1H NMR (300 MHz, $CDCl_3$) δ 3.52 (dd, 2 H, J = 16.5, 11.4 Hz), 2.78 (dd, 2 H, J = 15.9, 4.8 Hz), 1.48 (s, 3 H); MS (EI) *m/z* (rel intensity) 106 $[M]^+$ (20), 86 (24), 84 (37), 79 (32), 77 (100), 71 (21), 57 (24); HRMS *m/z* calcd for C_4H_7OCl 106.0185, found 106.0184.



35

1,1'-(6,6'-(2-Hydroxy-2-methylpropane-1,3-diyl)bis(oxy)bis(2-hydroxy-6,1-phenylene))diethanone (35). A solution of 2',6'-dihydroxyacetophenone **(28)** (2.0 g, 13.1 mmol) and 2-methyl-epichlorohydrin **(34)** (0.742 mL, 7.0 mmol) in hot i-PrOH (50.0 mL) was treated with a solution of KOH (0.465 g, 8.28 mmol) in i-PrOH (5.0 mL) and H_2O (1.0 mL). The reaction mixture was refluxed for 48 h and once cooled H_2O (50.0 mL) was added. The precipitates was filtered off and washed with ether and H_2O. The resultant solid was recrystallized from i-PrOH to give 0.784 g (2.09 mmol, 30%) of **35** as a tan colored solid: Mp

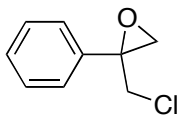
171.2 – 177.0 ^{o}C (EtOH); IR (ATR) (neat) 3463, 1618, 1590, 1457, 1446, 1418, 1362, 1340, 1299, 1282, 1230, 1191, 1178, 1103, 1075, 1029, 958, 943 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.7 (s, 2 H), 7.29 (t, 2 H, *J* = 8.1 Hz), 6.56 (d, 2 H, *J* = 8.4 Hz), 6.49 (d, 2 H, *J* = 8.1 Hz), 5.18 (s, 1 H), 4.01 (d, 2 H, *J* = 10.8 Hz), 3.94 (d, 2 H, *J* = 9.3 Hz), 2.53 (s, 6 H), 1.31 (s, 3 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 203.6, 159.7, 158.6, 134.1 114.3, 109.6, 103.0, 73.2, 70.2, 33.2, 22.6; MS (ES) *m/z* (rel intensity) 398 $[M + 1 + Na]^+$ (3), 397 $[M + Na]^+$ (100), 398, 365 (3), 212 (4), 195 (5), 119 (5); HRMS (ES) *m/z* calculated for $C_{20}H_{22}O_7Na$ 397.1263, found 397.1300.



36

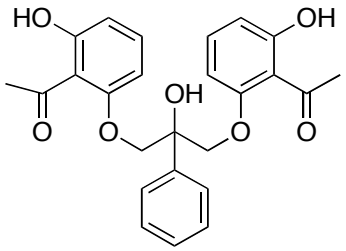
Diethyl-5,5'-(2-hydroxy-2-methylpropane-1,3-diyl)bis(oxy)bis(4-oxo-4H-chromene-2-carboxylate) (36). Sodium metal (0.122 g, 5.3 mmol) was dissolved in EtOH (7.0 mL) and heated to reflux. To the hot solution was added solid bis-phenol **35** (0.200 g, 0.534 mmol) and diethyl oxalate **(31)** (0.443 mL, 3.2 mmol). After refluxing for 20 h, the cooled reaction mixture was poured into ether and filtered. The solid was then added to water (6.0 mL) and acidified with 1M HCl (1.0 mL). The aqueous mixture was extracted with CH_2Cl_2. The organic extracts were combined and concentrated. To this resultant residue was added conc. HCl (0.5 mL) and heated in an oil bath for 5 min. The mixture was filtered and solid residue was purified by column chromatography on SiO_2 (R_f = 0.26, CH_2Cl_2/MeOH, 95:5) to give 0.115 g (0.534 mmol, 41%) of

36 as a brown oil: IR (ATR) (neat) 3468, 3458, 3090, 2976, 2980, 1735, 1646, 1603, 1476, 1450, 1249, 1219, 1105, 1073 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 7.57 (t, 2 H, *J* = 8.4 Hz), 7.13 (d, 2 H, *J* = 8.4 Hz), 6.96 (s, 2 H), 6.90 (d, 2 H, *J* = 8.1 Hz), 4.45 (q, 4 H, *J* = 13.8, 6.9 Hz), 4.45 (d, 2 H, *J* = 8.7 Hz), 4.12 (d, 2 H, *J* = 8.7 Hz), 1.53 (s, 3 H), 1.42 (t, 6 H, *J* = 6.9 Hz); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.4, 160.4, 158.7, 157.6, 135.0, 116.1, 115.3, 110.8, 109.2, 73.3, 71.3, 63.0, 21.4, 14.1; MS (ES) *m/z* (rel intensity) 562 $[M + 1 + Na]^+$ (5), 561 $[M + Na]^+$ (100); HRMS (ES) *m/z* calcd for $C_{28}H_{26}O_{11}Na$ 561.1373, found 561.1344.



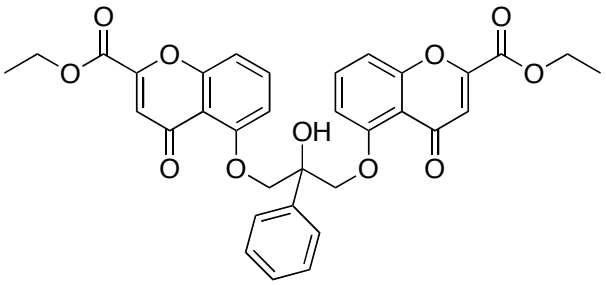
38

2-(Chloromethyl)-2-phenyloxirane (38).[56,57] A solution of benzoyl chloride **(37)** (1.65 mL, 14.2 mmol), LiBr (2.84 g, 32.7 mmol), chloroiodomethane (2.43 mL, 32.7 mmol) in dry THF (60.0 mL) was cooled to -78 ^oC and treated with *n*-BuLi (27.3 mL) dropwise over 20 min. After stirring for 1 h at -78 ^oC, the reaction mixture was warmed to rt and then concentrated in vacuo. The resultant red-orange residue was dissolved in hexanes and washed with saturated NH_4Cl solution, saturated sodium thiosulfate solution and brine. The organic extracts were dried (Na_2SO_4) and concentrated in vacuo. The residual solvent was then distilled (70 ^oC) out of the reaction mixture to give 1.96 g (11.6 mmol, 82%) of **38** as an orange liquid: ^1H NMR (500 MHz, $CDCl_3$) δ 7.45 (m, 2 H), 7.38 (m, 3 H), 4.06 (d, 1 H, *J* = 7.2 Hz), 3.86 (d, 1 H, *J* = 7.2 Hz), 3.22 (d, 1 H, *J* = 3.0 Hz), 2.94 (d, 1 H, *J* = 3.3 Hz); MS (EI) *m/z* (rel intensity) 170 $[M + 2]^+$ (36), 169 $[M + 1]^+$ (48), 168 $[M]^+$ (93), 167 (100), 163 (30), 133 (11), 105 (14), 104 (27), 103 (46), 91 (22), 96 (21); HRMS (EI) *m/z* calcd for C_9H_9OCl 168.0342, found 168.0350.



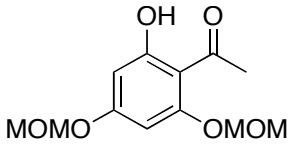
39

1,1'-(6,6'-(2-Hydroxy-2-phenylpropane-1,3-diyl)bis(oxy)bis(2-hydroxy-6,1-phenylene))diethanone (39). A solution of 2,6-Dihydroxyacetophenone **(28)** (2.0 g, 13.1 mmol) and 2-phenyl-epichlorohydrin (**38)** (1.2 mL, 7.0 mmol) in hot i-PrOH (50.0 mL) was heated to reflux and treated with a solution of KOH (0.465 g, 8.28 mmol) in i-PrOH (5.0 mL) and H_2O (0.5 mL). After refluxing for 48 h, H_2O (50.0 mL) was added to the cooled reaction mixture. The resultant precipitate was filtered off and washed with ether and H_2O. The crude residue was recrystallized from i-PrOH to give 0.632 g (1.49 mmol, 21%) of **39** as a tan solid: Mp 165.0 ^{o}C (dec) (CH_2Cl_2); IR (ATR) (neat) 3474, 3494, 2956, 2928, 2892, 2874, 2635, 1616, 1590, 1576, 1454, 1437, 1366, 1344, 1301, 1224, 1101, 1083 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) δ 11.9 (s, 2 H), 7.62 (d, 2 H, *J* = 7.5 Hz), 7.34 (m, 5 H), 6.58 (d, 2 H, *J* = 8.4 Hz), 6.49 (d, 2 H, *J* = 9.0 Hz), 5.95 (s, 1 H), 4.38 (s, 4 H), 2.27 (s, 6 H); ^{13}C NMR (75 MHz, DMSO-d_6) δ 204.3, 160.5, 159.1, 142.7, 134,8, 128.3, 127.6, 126.5, 114.2, 110.1, 103.3, 74.9, 74.1, 33.4; MS (ES) *m/z* (rel intensity) 460 $[M + 1 + Na]^+$ (5), 459 $[M + Na]^+$ (100), 425 (5), 316 (5); HRMS (ES) *m/z* calcd for $C_{25}H_{24}O_7Na$ 459.1420, found 459.1444.



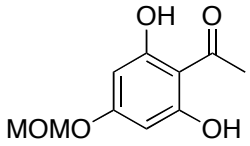
40

Diethyl 5,5'-(2-hydroxy-2-phenylpropane-1,3-diyl)bis(oxy)bis(4-oxo-4*H*-chromene-2-carboxylate) (40). Sodium metal (0.184 g, 8.01 mmol) was dissolved in EtOH (10.0 mL) and heated to reflux. To the hot solution was added **39** (0.350 g, 0.801 mmol) and diethyl oxalate **(31)** (0.666 mL, 4.81 mmol) and refluxed for 20 h. Once cooled, the reaction mixture was poured into ether and filtered. The solid was then added to water (6.0 mL) and acidified with 1 M HCl (1.0 mL). The aqueous mixture was extracted with CH_2Cl_2 and the organic extracts were combined and concentrated. To this resultant residue was added conc. HCl (0.5 mL) and heated in an oil bath. After 5 min, the solid was filtered and collected. The resultant residue was purified by column chromatography on SiO_2 (R_f = 0.10, CH_2Cl_2/MeOH 98:2) to give 0.0203 g (0.0340 mmol, 4.2%) of **40** as a white film: IR (ATR) (neat) 3479, 3468, 3492, 3455, 3081, 2959, 2928, 1733, 1629, 1606, 1569, 1457, 1449, 1437, 1418, 1384, 1362, 1327, 1251, 1062 cm^{-1}; ^1H NMR (300 MHz, DMSO-d_6) δ 8.02 (d, 2H, *J*= 8.4 Hz), 7.57 (t, 2H, *J*= 8.4 Hz), 7.39 (t, 3H, *J*= 6.9 Hz), 7.14 (d, 2H, *J*= 8.4 Hz), 7.00 (s, 2H), 6.93 (d, 2H, *J*= 8.1), 4.88 (d, 2H, *J*= 8.7), 4.46 (q, 4H, *J*= 7.2, 14.1 Hz), 4.36 (d, 2H, *J*= 8.7 Hz), 1.44 (t, 6H, 6.9); ^{13}C NMR (75 MHz, DMSO-d_6) δ 178.3, 160.5, 158.6, 157.6, 150.7, 134.9, 128.4, 128.2, 125.8, 127.6, 125.8, 116.3, 115.5, 111.0, 109.6, 73.8, 63.0, 14.1; MS (ES) *m/z* (rel intensity) 624 $[M + 1+ Na]^+$ (10), 623 $[M + Na]^+$ (100); HRMS (ES) *m/z* calcd for $C_{33}H_{28}O_{11}Na$ 623.1529, found 623.1487.



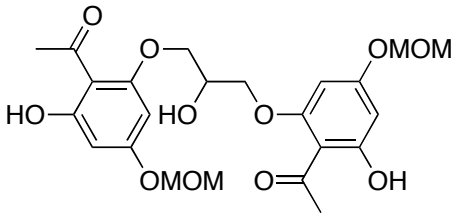
42

1-(2-Hydroxy-4,6-bis(methoxymethoxy)phenyl)ethanone (42).[59,60,109] A solution of 2,4,6-trihydroxyacetophenone **(41)** (13.0 g, 77.3 mmol) in CH_2Cl_2 (200 mL) was cooled to 0 ^oC. To the reaction mixture was added DIPEA (28.2 mL, 162.4 mmol) and stirred for 15 min. Then MOMCl solution[61] (24.7 mL, 162 mmol) was added dropwise at 0 ^oC and allowed to warm to rt. The reaction mixture was stirred for 3 h and poured into H_2O. The reaction mixture extracted with $CHCl_3$ and the organic extracts were combined, washed with water and brine and then dried ($MgSO_4$). The reaction mixture was then concentrated in vacuo and resultant orange oil was filtered through a pad of silica gel (R_f = 0.40, 4:1 Hex/EtOAc; Hex/EtOAc, 9:1) to give 5.7 g (22.2 mmol, 29%) of **42** as a white solid: Mp 44.3 - 49.1 ^oC; IR (ATR) (neat) 3129, 3110, 2959, 2945, 2937, 1612, 1590, 1411, 1415, 1360, 1265, 1219, 1206, 1165, 1077, 1062, 1023, 941, 926 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 13.7 (s, 1 H), 6.26 (d, 1 H, J = 2.4 Hz), 6.24 (d, 1 H, J = 2.4 Hz), 5.25 (s, 2 H), 5.17 (s, 2 H), 3.52 (s, 3 H), 3.47 (s, 3 H), 2.65 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) 203.3, 166.8, 163.5, 160.4, 106.9, 97.1, 94.5, 94.0, 56.7, 56.5, 33.1; MS (EI) *m/z* (rel intensity) 257 $[M + 1]^+$ (14), 256 $[M]^+$ (100), 211 (9), 182 (100), 152 (11), 86 (62), 84 (100), 69 (24), 57 (34); HRMS (EI) *m/z* calcd for $C_{12}H_{16}O_6$ 256.0947, found 256.0939.



43

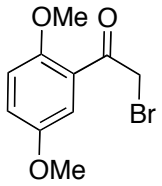
1-(2,6-Dihydroxy-4-(methoxymethoxy)phenyl)ethanone (42).[58-60] A solution of MOM-ether **42** (5.2 g, 20.3 mmol) in MeOH (200 mL) was treated with iodine (2.0 g, 7.87 mmol, 1% w/v) and stirred at rt for 17 h. The reaction mixture was quenched with sodium thiosulfate solution and extracted with ether. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant residue was purified by column chromatography on SiO_2 (R_f = 0.30 Hex/EtOAc 4:1, Hex/EtOAc, 4:1, 1:1) to give 1.79 g (8.44 mmol, 42%) of **43** as a yellow solid: Mp 119.5 – 125.4 ^oC (CH_2Cl_2); IR (ATR) (neat) 3278, 3271, 3259, 3254, 3014, 2973, 2931, 1620, 1582, 1433, 1359, 1277, 1249, 1221, 1215, 1142, 1066, 1055, 952 cm^{-1}; ^1H NMR (300 MHz, $CDCl_3$) δ 6.08 (s, 2 H), 5.16 (s, 2 H), 3.47 (s, 3 H), 2.70 (s, 3 H), 1.90 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 203.7, 163.3, 105.8, 96.0, 94.0, 56.4, 32.8; MS (EI) *m/z* (rel intensity) 213 $[M + 1]^+$ (13), 212 $[M]^+$ (100), 197 (12), 180 (22), 167 (40), 152 (20), 138 (32), 121 (7), 84 (15), 68 (31); HRMS (EI) *m/z* calcd for $C_{10}H_{12}O_5$ 212.0685, found 212.0683.



44

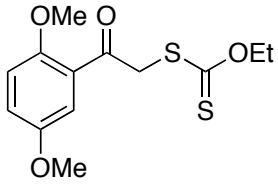
1,1'-(6,6'-(2-Hydroxypropane-1,3-diyl)bis(oxy)bis(2-hydroxy-4-(methoxymethoxy)-6,1-phenylene))diethanone (43). To a 100 mL round-bottom flask was added MOM-ether 41 (1.69 g, 7.99 mmol) and epichlorohydrin **(29)** (0.335 mL, 4.24 mmol) and dissolved in hot i-PrOH (30.0 mL). The reaction mixture was heated to reflux and to the solution was added a solution of KOH (0.282 g, 5.0 mmol) in i-PrOH (5.0 mL) and H_2O (1.0 mL). The reaction mixture was refluxed for 46 h and once cooled H_2O (50.0 mL) was added. The precipitate was filtered off and washed with ether and H_2O. The resultant solid was recrystallized from hot i-PrOH and dried overnight to give 0.630 g (1.31 mmol, 31%) of **44** as a pale yellow solid: Mp 149.2 – 157.6 ^{o}C (EtOH); IR (ATR) (neat) 3567, 3574, 3120, 3110, 2954, 2924, 2907, 1610, 1586, 1444, 1428, 1413, 1362, 1262, 121, 1148, 1126, 1109, 1087, 1060, 1021, 937 cm^{-1}; ^{1}H NMR (300 MHz, DMSO-d_6) 13.6 (S, 2H), 7.35 (s, 2H), 6.22 (d, 2H, *J*= 1.8 Hz), 6.14 (d, 2H, *J*= 2.1 Hz), 5.25 (s, 4H), 4.33 (br s, 1H), 4.16 (m, 4H), 3.37 (s, 6H), 2.63 (s, 6H); MS (EI) *m/z* (rel intensity) 481 $[M + 1]^+$ (10), 480 $[M]^+$ (30), 462 (6), 416 (9), 361 (11), 342 (9), 319 (10), 268 (14), 251 (17), 225 (37), 195 (43), 181 (67), 165 (65), 153 (47), 121 (22), 105 (13), 77 (21), 69 (35); HRMS *m/z* calcd for $C_{23}H_{28}O_{11}$ 480.1632, found 480.1628.

3.3 PLEUROTIN EXPERIMENTAL



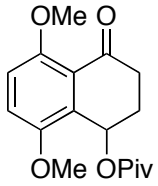
82

2-Bromo-1-(2,5-dimethoxyphenyl)ethanone (82).[110] A 500 mL flame dried round bottom flask was charged with 2',5'-dimethoxyacetophenone **(81)** (50.0 g, 275 mmol) and diluted with a solution of 2:1 diethyl ether/1,4-dioxane (150 mL). As the reaction was stirred bromine (14.2 mL, 275 mmol) was added dropwise via an addition funnel over 30 min. Stirring continued for 1h after the addition was complete and the reaction mixture was partitioned with H_2O and extracted with ether. The organic extracts were dried ($MgSO_4$) and concentrated to give crude product **82** as grayish-white solid. The crude solid was clean by ^1H NMR and carried on to next reaction without purification: ^1H NMR (300 MHz, $CDCl_3$) δ 7.38 (d, 1 H, J = 3.3 Hz), 7.10 (dd, 1 H, J = 9.0, 3.3 Hz), 6.95 (d, 1 H, J = 9.0 Hz), 4.64 (s, 2 H), 3.93 (s, 3 H), 3.82 (s, 3 H); MS (EI) *m/z* (rel intensity) 260 $[M + 2]^+$ (66), 258 $[M]^+$ (67), 244 (50), 243 (52), 166 (10), 165 (100), 150 (5), 122 (7), 107 (7), 92 (6), 77 (9), 63 (5); HRMS (EI) *m/z* calcd for $C_{10}H_{11}BrO_3$ 257.9892, found 257.9889.



84

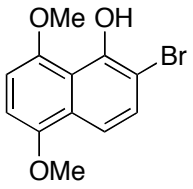
***S*-2-(2,5-Dimethoxyphenyl)-2-oxoethyl-*O*-ethylcarbonodithioate (84).**[100] A solution of compound **82** (65.2 g, 251 mmol) in acetone (500 mL) was cooled to 0 ^{o}C and treated with potassium ethyl xanthate **(83)** (41.2 g, 257 mmol). After stirring at rt for 5 h. The reaction mixture was concentrated and the resultant residue was partitioned with H_2O/ CH_2Cl_2. The organic extracts were combined, washed with H_2O and then dried ($MgSO_4$) and concentrated. The resultant residue was recrystallized with CH_2Cl_2/Hexanes to give 68.0 g (226 mmol, 90%) of **84** as yellow/brown solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.32 (d, 1 H, *J* = 3.3 Hz), 7.08 (dd, 1 H, *J* = 9.2, 3.3 Hz), 6.94 (d, 1 H, *J* = 9.3 Hz), 4.62 (q, 2 H, *J* = 7.2 Hz), 4.62 (s, 2 H), 3.92 (s, 3 H), 3.80 (s, 3 H), 1.40 (dd, 3 H, *J* = 7.2, 7.2 Hz); MS (EI) *m/z* (rel intensity) 300 $[M]^+$ (15), 267 (7), 243 (10), 211 (6), 166 (10), 165 (100), 122 (5), 107 (7), 77 (5), 57 (7); HRMS (EI) *m/z* calcd for $C_{13}H_{16}O_4S_2$ 300.0490, found 300.0482.



86

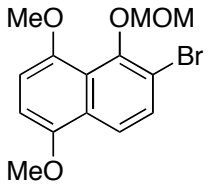
5,8-Dimethoxy-4-oxo-1,2,3,4-tetrahydronaphthalen-1-yl pivalate (86).[100] A solution of xanthate **84** (83.0 g, mmol) in 1,2-dichloroethane (400 mL) was treated with vinyl pivalate **(85)** (71.5 mL, mmol) and heated to reflux. After refluxing for 15 min, lauroyl peroxide (DLP) (11.2 mL, mmol) was added to the reaction mixture. Two additional portions of DLP (5.6 g, mmol) were added every 1.5 h. Refluxing continued for 2 h after the final addition of DLP and the reaction flask was cooled to room temperature and concentrated on the rotary evaporator. The resultant crude mixture was dissolved in 1,2-dichloroethane (800 mL) and the reaction mixture was heated to reflux again. DLP (92.0 g, 231 mmol) was added portion-wise over 5 h (18.4 g every 1 hour). After a total of 6 hrs of refluxing, the reaction mixture was cooled to rt and then in an ice water bath (20 min). The reaction mixture was concentrated in vacuo and the crude reaction mixture was purified via flash chromatography on SiO_2 (R_f = 0.50, Hex/EtOAc 9:1, 4:1, 1:1) to give 31.1 g (226 mmol, 41%) of **86** as a dark red oil/foam over the two steps: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.08 (d, 1 H, *J* = 9.3 Hz), 7.0 (d, 1 H, *J* = 9.0 Hz), 6.34 (t, 1 H, *J* = 2.7 Hz), 3.89 (s, 3 H), 3.80 (s, 3 H), 2.85 (ddd, 1 H, *J* = 16.8, 5.1, 5.1 Hz), 2.56 (ddd, 1 H, *J* = 16.8, 16.8, 4.8 Hz), 2.36 (dddd, 1 H, *J* = 14.7, 14.4, 3.0, 2.7 Hz), 2.20 (ddd, 1 H, *J* = 15.0, 14.1, 3.6, 3.3 Hz), 1.20 (s, 9 H); MS (EI) *m/z* (rel intensity) 307 $[M + 1]^+$ (6), 306 $[M]^+$ (30), 221 (10), 206 (11),

205 (72), 194 (7), 177 (12), 137 (12), 95 (12), 86 (67), 84 (100), 81 (40), 73 (16), 69 (87), 60 (15), 57 (56); HRMS (EI) *m/z* calcd for $C_{17}H_{22}O_5$ 306.1467, found 306.1464.



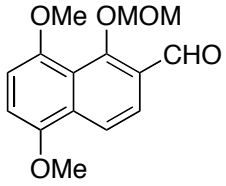
87

2-Bromo-5,8-dimethoxynaphthalen-1-ol (87).[100,111] A solution of pivalate **86** (14.0 g, 38.8 mmol) in dry CH_2Cl_2 (200 mL) was cooled to 0 ^oC for 10 min and treated with pyridinium bromide perbromide (3.28 g, 38.8 mmol). The reaction mixture was stirred at 0 ^oC for 2.5 h and diluted with CH_2Cl_2. The reaction mixture was washed with saturated sodium thiosulfate solution and the organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The crude residue was purified via flash column chromatography on SiO_2 (R_f = 0.65, Hex/EtOAc, 4:1) to give 5.20 g (18.4 mmol, 47%) of **87** as brown solid: Mp 125.0-136.3 ^oC (EtOAc); IR (ATR) (neat) 3330, 2940, 2838, 1610, 1504, 1454, 1390, 1299, 1253, 1165, 1151, 1126, 1088, 1050 cm $^{-1}$; ^1H NMR (300 MHz, $CDCl_3$) δ 10.2 (s, 1 H), 7.60 (d, 1 H, *J* = 9.0 Hz), 7.54 (d, 1 H, *J* = 9.0 Hz), 6.71 (d, 1 H, *J* = 8.4 Hz), 6.64 (d, 1 H, *J* = 8.4 Hz), 4.01 (s, 3 H), 3.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.1, 151.0, 149.7, 131.4, 127.8, 116.7, 114.8, 106.1, 105.4, 104.1, 57.2, 56.3; MS (EI) *m/z* (rel intensity) 283 $[M]^+$ (62), 282 (63), 269 (62), 267 (66), 254 (12), 218 (18), 204 (23), 189 (29), 165 (14), 132 (20), 115 (15), 97 (22), 87 (100), 81 (29), 73 (47), 69 (64), 60 (44), 57 (78), 55 (71); HRMS (EI) *m/z* calcd for $C_{12}H_{11}BrO_3$ 281.9892, found 281.9880.



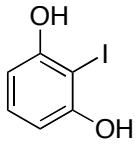
88

2-Bromo-5,8-dimethoxy-1-(methoxymethoxy)naphthalene (88). A solution of bromide **87** (5.20 g, 18.4 mmol) in dry THF (75.0 mL) was cooled to 0 ^{o}C and treated with sodium hydride (1.17 g, 48.8 mmol). The reaction was stirred for 30 min at 0 ^{o}C and then MOMCl solution (6.98 mL, 46.0 mmol) was added dropwise via syringe. The reaction mixture was warmed to rt and stirred for 15 h. The reaction was quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic extracts were dried ($MgSO_4$) and concentrated in vacuo. The resultant residue was purified via flash chromatography on SiO_2 (R_f = 0.70, Hex/EtOAc, 9:1) to give 4.90 g (15.0 mmol, 82%) of **88** as orange/brown oil: IR (neat) 2993, 2937, 2916, 2833, 2799, 1616, 1579, 1454, 1439, 1413, 1401, 1340, 1316, 1305, 1256, 1237, 1211, 1193, 1159, 1137, 1087, 1040, 978, 952 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.92 (d, 1 H, *J* = 9.0 Hz), 7.61 (d, 1 H, *J* = 9.0 Hz), 6.81 (d, 1 H, *J* = 8.7 Hz), 6.73 (d, 1 H, *J* = 8.4 Hz), 5.13 (s, 2 H), 3.94 (s, 3 H), 3.91 (s, 3 H), 3.75 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 150.5, 149.9, 149.5, 130.7, 128.7, 122.6, 120.4, 117.1, 108.1, 104.9, 101.6, 59.0, 57.5, 56.4; MS (EI) *m/z* (rel intensity) 328 $[M + 2]^+$ (60), 327 $[M +1]^+$ (60), 297 (25), 296 (25), 284 (14), 281 (23), 267 (17), 248 (24), 247 (100), 232 (11), 215 (30), 202 (34), 195 (23), 187 (38), 174 (53), 156 (15), 115 (17), 101 (12), 69 (13); HRMS (EI) *m/z* calcd for $C_{14}H_{15}BrO_4$ 326.0154, found 326.0143.



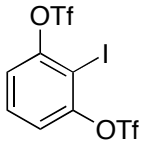
79

5,8-Dimethoxy-1-(methoxymethoxy)-2-naphthaldehyde (79). A solution of compound **88** (3.50 g, 10.7 mmol) in dry THF (40.0 mL) was cooled to -78 ^{o}C and treated with a 1.7 M solution of *t*-butyl lithium (17.0 mL, 28.9 mmol). After stirring for 1 hr at -78 ^{o}C, anhydrous DMF (5.22 mL, 67.4 mmol) was added dropwise and stirred at -78 ^{o}C for 30 min and then warmed to rt. The reaction mixture was cooled to 0 ^{o}C and quenched with saturated NH_4Cl solution and extracted with EtOAc. The organic extracts were washed with brine, dried ($MgSO_4$), and concentrated in vacuo. The resultant residue was purified via flash chromatography on SiO_2 (R_f = 0.75, Hex/EtOAc, 3:1) to give 1.31 g (9.63 mmol, 49%) of **73** as a yellow gum: IR (neat) 2934, 2855, 2360, 1738, 1681, 1617, 1602, 1581, 1509, 1459, 1415, 1349, 1260, 1234, 1156, 1104, 1050 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 10.6 (s, 1 H), 8.11 (d, 1 H, *J* = 8.7 Hz), 7.87 (d, 1 H, *J* = 9.0 Hz), 6.90 (d, 1 H, *J* = 8.7 Hz), 6.85 (d, 1 H, *J* = 8.4 Hz), 5.20 (s, 2 H), 3.97 (s, 6 H), 3.61 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 192.0, 159.7, 151.2, 150.3, 132.3, 128.3, 123.0, 120.6, 119.7, 107.9, 107.5, 102.8, 58.8, 57.2, 56.6; MS (EI) *m/z* (rel intensity) 277 $[M + 1]^+$ (18), 276 $[M]^+$ (100), 264 (10), 245 (18), 232 (90), 231 (85), 230 (40), 217 (92), 216 (61), 202 (82), 201 (65), 187 (28), 175 (39), 143 (19), 115 (48), 97 (29), 89 (33), 81 (41), 71 (44), 63 (26), 57 (92); HRMS (EI) *m/z* calcd for $C_{15}H_{16}O_5$ 276.0998, found 276.0998.



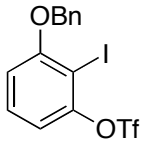
111

2-Iodoresorcinol (111).[112] A 250 mL round bottom flask was equipped with large elliptical stir bar and open to the atmosphere was charged with distilled water (46.0 mL), resorcinol **107** (7.27 g, 66.0 mmol) and iodine (17.9 g, 70.6 mmol), and placed in an ice-water bath. The reaction mixture was stirred vigorously and $NaHCO_3$ (6.15 g, 73.3 mmol) was added portion-wise via spatula (50.0 mg every 5-10 seconds) over 5 minutes (CO_2 gas evolution was observed upon addition). The ice bath was removed and the reaction mixture was warmed to rt over 20 min and stirred for an additional 10 min. The reaction mixture was extracted with EtOAc and combined organic extracts were washed with 10% sodium thiosulfate and brine, dried (Na_2SO_4) and concentrated in vacuo. The resultant solid was triturated with $CHCl_3$ (20.0 mL) for 10 min at -10 ^oC (EtOH/ice bath), filtered, and washed with cold $CHCl_3$ to give 8.40 g (35.6 mmol, 54%) of 2-iodoresorcinol **(111)** as a cream-colored solid: ^1H NMR (300 MHz, $CDCl_3$) δ 8.87 (br s, 2 H), 7.00 (t, 1 H, J = 8.1 Hz), 6.47 (d, 2 H, J = 8.1 Hz); MS (EI) *m/z* (rel intensity) 236 $[M]^+$ (54), 218 (15), 128 (6), 127 (12), 110 (18), 109 (12), 63 (100), 55 (84); HRMS (EI) *m/z* calcd for $C_6H_5IO_2$ 235.9334, found 235.9338.



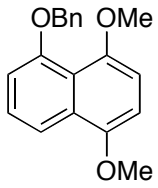
112

2-Iodo-1,3-phenylene-bis(trifluoromethanesulfonate) (112).[112] A solution of 2-iodoresorcinol **(111)** (5.90 g, 25.0 mmol) in dry CH_2Cl_2 (55.0 mL) was cooled to -78 ^oC with a dry-ice acetone bath and treated with DIPEA (10.4 mL, 60.0 mmol) via syringe pump over 5 min. Next triflic anhydride (8.5 mL, 50.0 mmol) was added via syringe pump over 15 min and stirring continued at -78 ^oC for ten min. The reaction mixture was warmed to 0 ^oC with an ice water bath over 1 h and then slowly quenched with water. The reaction mixture was extracted with CH_2Cl_2 and the combined organic extracts were washed with saturated aqueous sodium bicarbonate solution and brine, dried (Na_2SO_4), and concentrated in vacuo. The resultant oil was dissolved in 1:1 Ether/Hexanes (100 mL) and silica gel (3.60 g) was added and stirred at rt for 30 min. The slurry was then filtered and the silica cake was washed with 1:1 Hex/Ether (200 mL). The resultant organic filtrate was concentrated in vacuo to give 12.1 g (24.2 mmol, 97%) of **112** as brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (d, 1 H, J = 7.8 Hz), 7.54 (d, 1 H, J = 7.8 Hz), 7.38 (d, 1 H, J = 8.4 Hz); MS (EI) *m/z* (rel intensity) 502 $[M + 2]^+$ (13), 500 $[M]^+$ (100), 493 (10), 367 (90), 303 (25), 275 (15), 233 (9), 206 (12), 176 (9), 128 (7), 107 (35), 69 (25); HRMS (EI) *m/z* calcd for $C_8H_3O_6F_6S_2I$ 499.8320, found 499.8300.



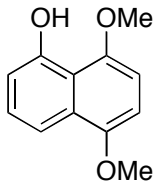
108

3-(Benzyloxy)-2-iodophenyl-trifluoromethanesulfonate (108).[107] To a 250 mL round-bottom flask with stir bar and reflux condenser was added compound **112** (12.0 g, 24.0 mmol) and dissolved in 1,2-Dimethoxyethane (85.0 mL). To the reaction flask was added Cs_2CO_3 (9.52 g, 29.2 mmol) and heated to 80 ^oC for 4 h. The reaction mixture was cooled to room temperature and to it was added BnBr (3.50 mL, 29.0 mmol). The reaction was stirred for 5 h and then quenched with saturated aqueous NH_4Cl solution and extracted with EtOAc. The combined organic extracts were washed with brine, dried (Na_2SO_4), and concentrated in vacuo. The resultant oil was purified via column chromatography on SiO_2 (R_f = 0.30, Hex/EtOAc, 4:1) to give 6.24 g (13.6 mmol, 57%) of **108** as amber/brown oil: ^1H NMR (300 MHz, $CDCl_3$) δ 7.55-7.31 (m, 6 H), 6.98 (d, 1 H, *J* = 8.1 Hz), 6.86 (d, 1 H, *J* = 8.1 Hz), 5.21 (s, 2 H); MS (EI) *m/z* (rel intensity) 459 $[M + 1]^+$ (8), 458 $[M]^+$ (42), 367 (10), 309 (13), 218 (10), 198 (21), 107 (51), 91 (100), 79 (32), 69 (57), 65 (75); HRMS (EI) *m/z* calcd for $C_{14}H_{10}F_3IO_4S$ 457.9297, found 457.9316.



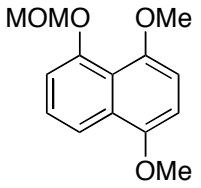
113

5-(Benzyloxy)-1,4-dimethoxynaphthaleneiodide (113). A solution of compound **108** (1.0 g, 2.30 mmol) and 2-methoxyfuran **(101)** (0.257 mL, 2.70 mmol) in dry THF (2.25 mL) was cooled to -78 ^{o}C and treated with a 1.6 M solution of *n*-BuLi (1.27 mL, 2.03 mmol) dropwise over 15 min. After stirring for 10 min at -78 ^{o}C, the reaction mixture was quenched with water and extracted with ether. The ethereal extracts were combined, dried ($MgSO_4$), and concentrated in vacuo. The resultant residue was chromatographed by flash column on SiO_2 (Hex/EtOAc, 4:1) to give the cycloaddition product. Once concentrated, the resultant solid was dissolved in acetone (24.0 mL) and treated with potassium carbonate (3.10 g, 22.6 mmol) and dimethylsulfate (2.10 mL, 22.6 mmol) and refluxed for 16 h. Once cool, the residual cesium carbonate salts were filtered out and the filtrate was concentrated in vacuo. The resultant residue was purified via flash chromatography on SiO_2 (R_f = 0.60 (1:1 Hex/EtOAc), Hex/EtOAc, 4:1) to give 0.485 g (1.65 mmol, 73%) of **113** as white solid: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.89 (d, 1 H, *J* = 8.4 Hz), 7.60 (d, 1 H, *J* = 7.2 Hz), 7.43-7.32 (m, 3 H), 7.0 (d, 1 H, *J* = 7.5 Hz), 6.80 (d, 1 H, *J* = 8.4 Hz), 6.74 (d, 1 H, *J* = 8.4 Hz), 5.21 (s, 2 H), 3.96 (s, 3 H), 3.89 (s, 3 H); MS (EI) *m/z* (rel intensity) 295 $[M + 1]^+$ (23), 294 $[M]^+$ (97), 204 (13), 203 (67), 185 (10), 175 (17), 160 (25), 115 (39), 91 (100), 65 (15), 55 (20); HRMS (EI) *m/z* calcd for $C_{19}H_{18}O_3$ 294.1256, found 294.1254.



115

5,8-Dimethoxynaphthalen-1-ol (115).[111,113,114] A solution of compound **113** (0.485 g, 1.60 mmol) in EtOAc (16.0 mL) was treated with 10.0 mol% Pd/C (0.177 g, 0.16 mmol) and stirred under H_2 atmosphere (balloon) at rt. After stirring for 4.5 h, there was no change by TLC. A second 0.1 eq. of Pd/C was added (0.170 g, 0.164 mmol) and 1 drop of AcOH. The reaction was stirred under H_2 atmosphere overnight. The reaction was filtered through celite and concentrated in vacuo. The resultant oil was purified by column chromatography on SiO_2 (R_f = 0.45 (1:1 Hex/EtOAc), Hex/EtOAc, 4:1) to give 0.230 g (1.13 mmol, 68%) of **115** as a white crystalline solid: Mp 98.1 – 102.0 ^oC (CH_2Cl_2); IR (ATR) (neat) 3332, 3090, 3017, 2965, 2943, 1769, 1612, 1513, 1392, 1239, 1230, 1205, 1170, 1161, 1140, 1096, 1034 cm $^{-1}$; ^1H NMR (500 MHz, $CDCl_3$) δ 9.48 (s, 1 H), 7.73 (dd, 1 H, *J* = 5.1, 0.6 Hz), 7.39 (t, 1 H, *J* = 4.8 Hz), 6.94 (dd, 1 H, *J* = 4.5, 0.6 Hz), 6.67 (dd, 1 H, *J* = 9.6, 5.1 Hz), 4.02 (s, 3 H), 3.96 (s, 3 H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 154.4, 150.3, 150.1, 128.4, 127.3, 115.6, 113.0, 111.4, 103.4, 103.0, 56.3, 55.8; MS (ES) *m/z* (rel intensity) 205 $[M + 1]^+$ (10), 204 (58), 203 (28), 195 (70), 191 (13), 190 (40), 189 (100), 175 (30), 174 (17), 159 (10), 119 (57); HRMS (ES) *m/z* calcd for $C_{12}H_{12}O_3$ 204.0786, found 204.0797.



89

1,4-Dimethoxy-5-(methoxymethoxy)naphthalene (89). A solution of compound **115** (0.229 g, 1.15 mmol) in dry THF (11.5 mL) was cooled to 0 ^{o}C and treated with NaH (0.0540 g, 1.35 mmol). After stirring at 0 ^{o}C for 30 min, the reaction mixture was treated with MOMCl solution[61] (0.450 mL, 1.57 mmol) and 5.0 mol % of TBAI (0.0140 g, 0.0563 mmol) and warmed to RT. After 2.5 h, the reaction mixture was quenched at 0 ^{o}C with saturated NH_4Cl solution and extracted with ether. The organic extracts were combined, washed with brine, dried ($MgSO_4$) and concentrated in vacuo. The crude reside was purified by column chromatography on SiO_2, (R_f = 0.8 (1:1 Hex/EtOAc), Hex/EtOAc, 9:1) to give 0.265 g (1.07 mmol, 95%) of **89** as a white solid: Mp 78.6 – 84.2 ^{o}C; IR (ATR) (neat) 3079, 3066, 2984, 2956, 2939, 2915, 1588, 1517, 1459, 1411, 1383, 1368, 1277, 1247, 1236, 1208, 1169, 1155, 1114, 1075, 1042, 990,965, 943 cm $^{-1}$; ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (d, 1 H, *J* = 8.4 Hz), 7.39 (t, 1 H, *J* = 15.9, 7.8 Hz), 7.15 (d, 1 H, *J* = 7.8), 6.80 (d, 1 H, *J* = 8.4 Hz), 6.73 (d, 1 H, *J* = 8.4 Hz), 5.26 (s, 2 H), 3.96 (s, 3 H), 3.92 (s, 3 H), 3.62 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 153.6, 150.5, 149.7, 129.0, 125.8, 119.6, 116.8, 114,8, 107.0, 104.0, 97.1, 57.3, 56.4, 55.8; MS (EI) *m/z* (rel intensity) 249 $[M + 1]^+$ (15), 248 $[M]^+$ (100), 218 (20), 204 (19), 203 (55), 189 (22), 160 (22), 115 (48), 102 (18), 91 (73), 85 (27), 81 (22), 71 (39), 69 (52), 57 (69), 55 (37); HRMS (EI) *m/z* calcd for $C_{14}H_{16}O_4$ 248.1049, found 248.1042.

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